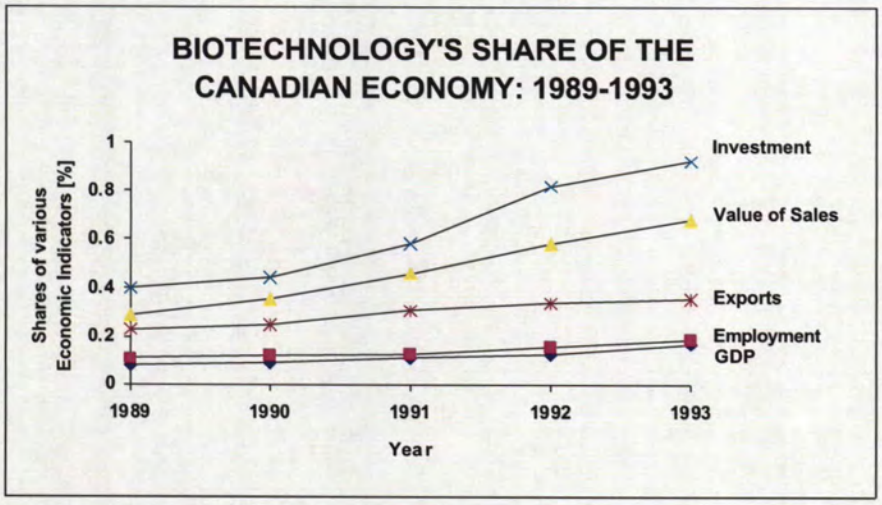
BACKGROUND ECONOMIC STUDY

of the

CANADIAN BIOTECHNOLOGY INDUSTRY



Submitted to:

Environment Canada and Industry Canada

Submitted by:

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212 King Street West, Suite 500
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June 1995

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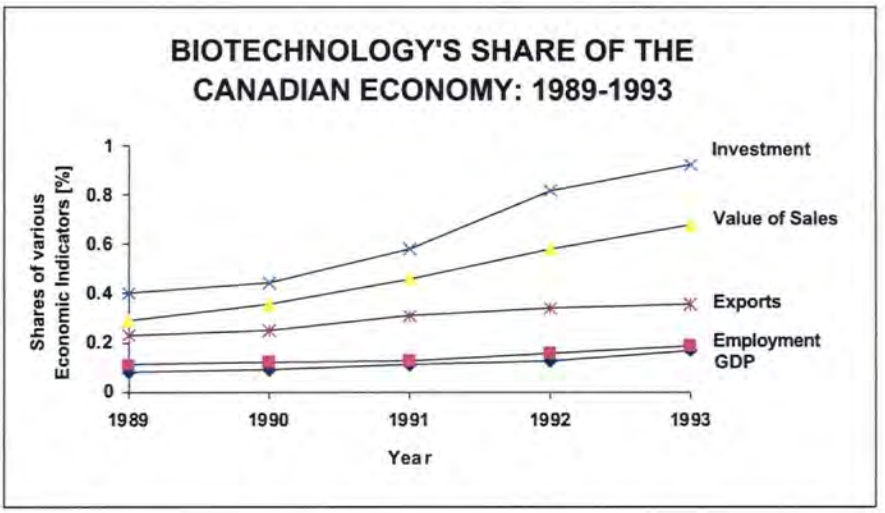

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This research was commissioned by Industry Canada and Environment Canada. The views expressed are those of the author, and do not necessarily reflect the policy of the Government of Canada. It is hoped that this paper will encourage a more informed public discussion on the economic significance and future challenges of the biotechnology industry.

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ACKNOWLEDGMENTS

I wish to acknowledge with gratitude the contributions of the following members of the research team for this study. John Newall and Joanne Kirley led the market research team from Canada Market Research Ltd. Steve Edmonds of Lawrence & Milley Consultants and his associates contributed to the survey design and conducted some industry interviews. Eileen McMahon of Deeth Williams Wall conducted certain background interviews and assisted with the research and early drafting on intellectual property law. Dave Gannon of Zeneca BioProducts provided critical review and advice on early drafts of the environmental biotechnology chapter.

In addition to overall project management and participation in all aspects of the research, I wrote the later drafts of this study and am responsible for any errors of omission and commission appearing in it.

Jim Heller

EXECUTIVE SUMMARY

The federal government commissioned this study to provide background economic research to support the development of biotechnology policy, legislation and regulation including the National Biotechnology Strategy (NBS), *Patent Act* amendments and the drafting of biotechnology regulations under the *Canadian Environmental Protection Act* (CEPA).

CEPA defines biotechnology as "the application of science and engineering in the direct or indirect use of living organisms in their natural or modified forms" [CEPA, s. 3(1)]. The study has adopted the perspective of the public interest defined to include both the value-added contributions of biotechnology to the Canadian economy and its potential to improve the environment and the quality of life of Canadians. Readers should note that this background research study does not necessarily represent the views of the Government of Canada.

A myth prevails that biotechnology is something discrete or homogeneous, a corollary of which is the view that a "biotechnology industry" exists. This perception is facile but inaccurate. Biotechnology is really a catch-all term for a broad group of useful, enabling technologies with wide and diverse applications in industry and commerce. The CEPA definition encompasses processes as different as fish farming, forestry, the production of enzymes for laundry detergents and the genetic engineering of bacteria to clean up oil spills, kill insect larvae or produce insulin.

Biotechnology is myriad dissimilar processes, producing even greater numbers of dissimilar products for vastly dissimilar applications. These processes and products have so little in common that it is difficult to construct valid generalizations about them, for whatever purpose. Because of this lack of systematic, uniform characteristics, effective legislation cannot be homogeneous.[1]

Although the term "biotechnology industry" is used in the study title, consistent with its common usage, to reflect better the nature of biotechnology, the term "biotechnology community" has been adopted wherever possible throughout the text. This community is the real network which makes biotechnology tick in this country. It includes:

- **new biotechnology firms** (NBFs);
- **university departments** of microbiology and related disciplines;
- **research institutes** partially or fully engaged in biotechnology research;
- **established corporations** with biotechnology divisions;
- **venture capital firms**;
- **regulatory bodies**;
- **industrial associations**;

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[1] Miller, H.I. "Regulation." Chapter 12 in *The Genetic Revolution: Scientific Prospects and Public Perceptions.* Edited by B.D. Davis. Baltimore: The Johns Hopkins University Press, 1991.

- **scientific bodies**; and
- **suppliers** of equipment and materials.

This study examined seven issues identified by the NBS in 1991 that needed to be addressed to enhance Canada's international competitiveness in biotechnology.

1. **Financial Resources for Growing Companies:** The lack of equity financing inhibits commercial development and exposes Canadian firms to takeovers by foreign competitors.

2. **Human Resources:** There is a shortfall in highly qualified personnel with managerial, production, research and regulatory skills.

3. **Regulations:** Delays and uncertainties discourage investment, increase costs and undermine public confidence.

4. **Intellectual Property Protection:** Uncertainties in the patent system have delayed the commercialization of scientific discoveries.

5. **Infrastructure for Scientific Research:** The erosion of funding support for infrastructure maintenance and upgrading for university research has meant that Canada is losing its best graduate students to better equipped foreign facilities and is failing to attract sufficient students to the life sciences.

6. **Public Perception and Market Acceptance:** The public's perception of risks and benefits associated with specific commercial applications of new biotechnologies is important to the overall success of this pursuit in Canada.

7. **Strong Voice for Industry:** A strong, credible and respected voice and a supporting infrastructure can play an advocacy role for the biotechnology industry both nationally and internationally.

Overview of the Canadian Biotechnology Community

A survey of Canadian biotechnology firms was conducted to obtain reliable indicators of economic performance and overall contributions to the Canadian economy. The survey was a stratified random sample of 175 firms from a universe of 538 companies meeting the above definition of the Canadian biotechnology community. A total of 156 firms responded representing a response rate of 89 percent. Strata were defined by the number of employees per firm and firm categories. Economic analysis was conducted using a sectoral allocation method.

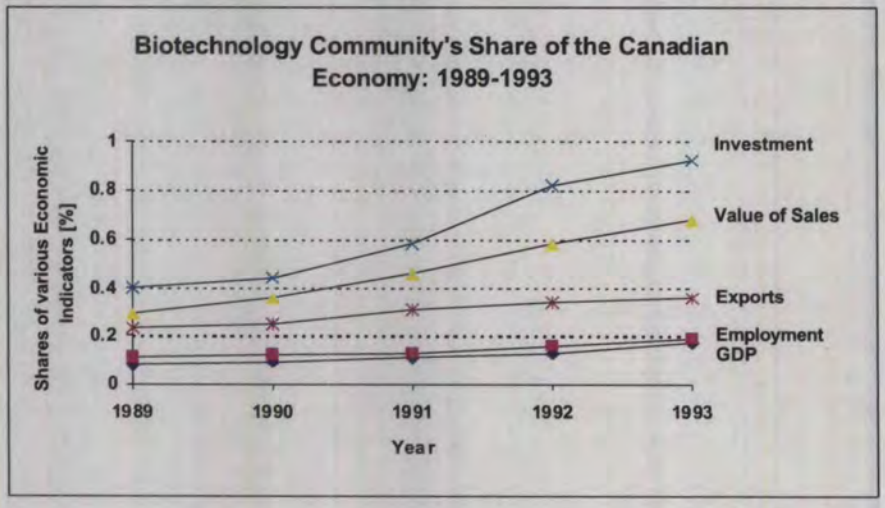
- Of the 538 firms, 147 (27 percent) are engaged in second generation biotechnology activities which include recombinant (rDNA) technologies as well as applications using process technology, chemistry and classical engineering.

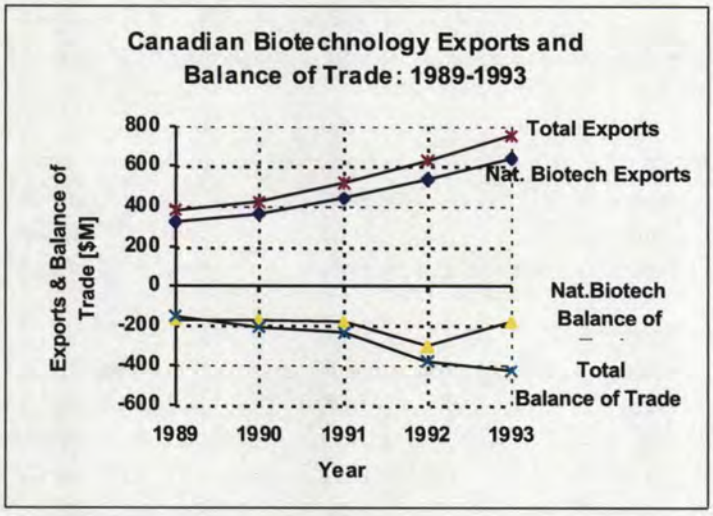
- Most firms are concentrated in Ontario, Quebec and British Columbia.
- Most have fewer than 10 employees (57 percent) and are privately owned (72 percent).
- The largest category is supplier firms (32 percent) followed by health care (22 percent), environment (13 percent), research institutes (12 percent) and resource and agri-food (11 percent each).
- Most private firms are privately held (73 percent) and Canadian owned (85 percent).
- In second generation biotechnology, most firm level business involves innovative intellectual property (IP) activity (56 percent) followed by generic (25 percent) and licensed (19 percent) IP activities.
- In 1993, there were 23,260 full-time equivalent persons (FTE) working in Canadian biotechnology. Of this total, 7,230 were employed in second generation work.
- In the rDNA area, health care employed 5,845 FTEs (81 percent), agriculture had 870 FTEs (12 percent) and the remaining 7 percent were distributed among several end use sectors (e.g., environment, pulp and paper, food and beverage).
- Over the 1989 to 1993 period, total Canadian biotechnology employment grew at a 14 percent per year rate, with the largest sector — health care — growing at an above industry pace of 17 percent per year. Agriculture and the food and beverage industry have shown more modest employment growth of 4 percent and 5 percent per year respectively.
- The total value of Canadian biotechnology sales in 1993 was $2,095 million of which $465 million (22 percent) was in rDNA activity. Most rDNA sales were in health care ($408 million) and agriculture ($50 million). Over the 1989 to 1993 period, total Canadian biotechnology sales grew at a remarkable 24 percent per year, with health care setting the pace at 27 percent per year. Agriculture and food and beverage sales grew at 17 percent and 8 percent per year respectively. Among the smaller sectors, environment literally exploded out of the starting blocks with a four-year growth rate averaging 80 percent per year (and 1993 sales of $67 million).
- Most 1993 investment in productive capacity was in the natural lifeform area ($207 million) with only $15 million spent on rDNA productive capacity. This underscores the critical importance of the NBS issue of financial help for Canadian NBFs. Productivity has remained steady in the natural lifeform biotechnology area in the range of $127,000 to $160,000 per FTE employee but has grown dramatically in the rDNA area from $35,000 per employee in 1989 to $122,000 per employee in 1993.

- Research and development (R&D) spending in Canadian biotechnology grew at a phenomenal pace of 41 percent per year over the 1989 to 1993 period. It reached $991 million in 1993 of which $312 million (31 percent) was in basic research and $332 million (34 percent) was in rDNA research. The health care sector accounted for most rDNA R&D spending ($256 million or 77 percent) with agriculture accounting for an additional $58 million (17 percent).

- Canadian biotechnology exports totalled $749 million in 1993 of which $109 million were rDNA based. Over the 1989 to 1993 period, overall exports grew at a 19 percent per year rate, with the rDNA portion growing at 21 percent per year. Most of the rDNA export growth was in health care ($63 million in 1993) with agricultural rDNA exports remaining steady at around $43 million. However, Canada is running a balance of trade deficit in both the natural (-$175 million in 1993) and rDNA portions (-$255 million in 1993) of the biotechnology business. The deficit is increasing primarily because of increases in the rDNA portion which is concentrated almost entirely in health care. Both the natural and rDNA trade figures for health care showed increasing deficits over the 1989 to 1993 period. The natural biotechnology trade deficit remains relatively flat because of offsetting positive growth from agriculture. The agbio trade on the rDNA side remains positive and steady within a $41 million to $46 million range.

The "good" news is that Canadian biotechnology's share of five aggregate economic indicators (GDP, employment, value of sales, investment and export earnings) showed rapid growth over the 1989 to 1993 period, during Canada's worst postwar recession. In fact, biotechnology's share of Canada's GDP, sales and investment more than doubled during these years. The "bad" news is that the biotechnology trade deficit grew almost threefold from -$147 million to -$430 million during the same period, driven primarily by health care imports.





The survey yielded additional economic data which can be found throughout the report. It also provided attitudinal information on issues of importance to the Canadian biotechnology community.

International Competitiveness

The study cites references estimating the global market for biotechnology in 1993 at US$36 billion. Of this:

- the biopharmaceutical portion was around $7.7 billion;
- industrial enzymes (e.g., food, detergents, diagnostics and fine chemicals) accounted for another $900 million;
- bioremediation was between $400 million to $500 million;
- veterinary vaccines added up to $1,060 million.

The global estimate probably includes considerable traditional biotechnology product sales in addition to rDNA-based products.

In biopharmaceuticals, market share was distributed among the United States, $3.1 billion (40 percent); Japan, $2.1 billion (28 percent); Europe, $2 billion (26 percent); and the rest of the world, including Canada, $0.5 billion (6 percent). Canada's share of global sales was $300 million (3.9 percent) which puts it well ahead of the commonly held view that the country is a "2 percent" pharmaceutical market.

Agbiotech products in the form of transgenic seeds, plants and produce are just beginning to enter the marketplace, but many products are expected to be commercialized over the next 10 years. One forecast places global agbiotech sales of these products at $2.1 billion by 2000 (with the U.S. share at $1.2 billion) and $8.8 billion by 2005 (with a projected U.S. share of $4.8 billion). Another forecast shows global microbial products with agricultural

applications reaching sales of $400 million to $600 million by 1995 (with U.S. sales of $170 million to $280 million) and $1.2 billion to $2.3 billion by 2005 (with U.S. sales of $600 million to $1,140 million).

Global bioremediation demand will also expand exponentially in the next decade, reaching around US$1 billion by the year 2000. Canada's share of the 1993 bioremediation market was US$49 million (about 10 percent to 12 percent). Canadian environmental biotechnology exporters should be able to expand the country's global share.

World leaders in biotechnology include the United States, Japan and certain European countries (Belgium, France, Germany, Italy, the Netherlands and the United Kingdom). East Asian countries will also establish a presence in the global biotechnology marketplace (e.g., China and Hong Kong). Canada should expect to be a major participant as well. Information on biotechnological activity in the other G-7 countries (United States, United Kingdom, France, Germany, Italy and Japan), other selected countries (Australia, Austria, Belgium, other East Asian countries and the Netherlands) and some important biotechnology firms in those countries is provided in Section 2.2 of this report. An emphasis is placed on U.S. industrial strategy favouring the biotechnology industry to reflect the dominant position of U.S. biotechnology in the world.

During the last 15 years, over 1,000 small to medium-sized U.S. NBFs have been started to develop or manufacture pharmaceuticals for human use. Some 200 are public companies. Corresponding figures in this report indicated that, in 1993, 94 Canadian health care biotechnology firms engaged in rDNA activity of which 19 were publicly traded companies. In 1992 and 1993, more than $11.5 billion of new external capital financing was raised by U.S. NBFs (not counting in-house biotechnology R&D by U.S.-established pharmaceutical corporations). Most of this investment took place in the United States although the sources of the investment capital were global.

U.S. federal government support for biomedical R&D, technology transfer policies and strong IP protection have created an environment conducive to discovery and commercialization of new therapeutic advances. Serious efforts have been made by the Food and Drug Administration (FDA) to rationalize the regulatory process and reduce delays in the approval process for biologics. Most important, the widespread existence of health insurance for prescription drugs in the United States and other industrialized countries (including Canada) has provided a dependable market for biotechnology drugs that is relatively unencumbered by patients' ability to pay. Together, these factors have made investment in research on new biotechnology-based health care products less costly, less risky and potentially more rewarding financially. They have also stimulated more private sector investment than would otherwise have happened.

The emergence of biopharmaceuticals was aided by the price-insensitive nature of the U.S. health care marketplace. This market is beginning to change, however. Health insurers are injecting more price sensitivity into prescribing and dispensing decisions. This trend has been called "managed care pharmacy" (MCP). A whole new industry of companies that manage the prescription drug benefits for U.S. employers and health insurers has sprung up

in the last five years or so. Many U.S. plans have adopted the generic substitution approach of Canadian provincial formularies. Even when there is no generic copy of a specific compound, close therapeutic substitutes may exist. Pharmaceutical benefit managers are attempting to force price competition among close substitutes by developing formularies and encouraging or requiring the prescribing of drugs in the formulary. This phenomenon is forcing pharmaceutical companies to compete on the basis of price as well as quality.

Representatives of Canadian biotechnology firms rated various factors affecting their companies' international competitiveness (including wage rates, quality of education, exchange rates, availability of trained personnel and sources of training). The reader is referred to the text (Section 2.3) for an analysis of responses, but should note that respondents from the environmental biotechnology industry rated most listed factors as disadvantages. Their views warrant serious examination. This sector is inherently disadvantaged for two fundamental reasons: as the "third wave"of biotechnology (the first two being health care and agriculture), it arrived at a moment when public funding support was under strain, and it needs environmental legislation and policy initiatives to generate the "market pull" inherently available to health care and agriculture. The issue is explored in the study but defines an area of concern for government policy makers.

The study looks at successful strategies adopted by Canadian biotechnology firms to enhance their ability to compete in world markets (Section 2.4). These include:

- management characteristics (skills, knowledge, contacts and coverage of R&D, regulation, manufacturing and finance);

- strategy (a strategic vision of product development, a strong market orientation, positive customer perception, detailed and systematic planning, efficient and fast development work, and R&D support systems); and

- the competitive environment (potential high-growth targeted markets and a network of relationships among producers and users of technology to implement the firm's strategy effectively).

Furthermore, a recent Canadian study of biotechnology companies found that managers of effective firms are often led by an inventor–entrepreneur characterized by innovative action. Ineffective firms, using a prestige logic, lack focus, rely on government support, spend on facilities without defined need and often have an incomplete management team. Successful strategies for biotechnology companies are developed by evaluating all the aforementioned strategic elements to determine optimal managerial actions. These methods are being used increasingly, both by Canadian financial firms and multinationals, to explore possible strategic alliances and to evaluate possible investments in NBFs.

Biotechnology Trends and Forecasts

The study reviews scientific and commercial developments in biotechnology over the last two decades as well as the current science in biopharmaceuticals, agri-food and environmental biotechnologies (Chapter 3). It signals the most likely food products to undergo rDNA modification to provide resistance to insects, virus and microorganisms; herbicide and stress tolerance; nutritional value; and controlled ripening (Section 3.3). The study also examines the biotechnology mechanisms to develop products addressing various animal production objectives (e.g., productivity, feed efficiency, alternative feeds, product composition, disease control/animal health, carcass quality and reproductive management and performance).

The study highlights Canada's advanced research program in forest biotechnology (viz., tissue culture) now awaiting successful technology transfer to private industry and the provinces. Biotechnology is making its most significant impact, in the short term, in the mining and energy sectors by economically resolving environmental problems resulting from industrial activity. In the longer term, biotechnology will develop processes, now under research, to optimize mineral or energy recovery. In the pulp and paper sector, biological wastewater treatment and enzyme treatments are used. Research to deploy fungi for biological bleaching and biomechanical pulping is under way. The application of these technologies has been facilitated by low cost, legislation and through supplier companies of enzyme treatments.

Low, median and high-growth scenarios are constructed to provide forecasts of the value of sales for Canadian biotechnology sectors (Section 3.4). The 10-year, median-growth forecast averages over 17 percent per year and is projected to yield sales of $10.5 billion by the year 2003. This growth is led by Canada's natural resource sectors — agri-food, environment and resources (including mining, energy, horticulture, pulp and paper, and forestry) — and is predicated on the development of a coherent national biotechnology strategy with government fiscal and policy stimuli.

In this scenario, health care will grow at a diminished pace because of insufficient capital availability (exacerbated by Canada's underlying fiscal climate) and pharmacoeconomic performance ("cost effectiveness"). If these assumptions hold, the agri-food sectors should capture the largest share of the Canadian biotechnology market sometime over the next 10 years. The 10-year, high-growth forecast averages over 25 percent per year and leads to sales by the year 2003 of $20.4 billion. It is predicated on greater than expected world demand for food and for bioremediation and other environmental biotechnology applications. On the other hand, the low-growth forecast averages just under 9 percent per year and assumes a sluggish investment climate, incoherence in national biotechnology strategy and a growing lack of acceptance, particularly of agri-food biotechnology products, by consumers. Employment in the median-growth scenario for Canadian biotechnology will lead to around 120,000 jobs within 10 years — a fivefold increase from present levels.

Commercialization of Biotechnology Products

The study examines the commercialization efforts of Canadian biotechnology firms (Chapter 4). Market opportunity or demand, in-house expertise and access to proprietary knowledge topped the list of key reasons for market entry by these firms. Market barriers included, in order, lack of financing, lack of market acceptance, Canadian regulatory barriers and labour availability. The chapter analyzes survey responses by sector and size of firm. These analyses are supplemented by material from in-depth interviews. The interviews flagged a number of important issues including capital availability, the importance of IP protection and maintaining confidentiality in industry-sponsored university research (Section 4.1).

Representative time lines for the commercialization of a typical therapeutic biopharmaceutical are developed and show that, for a patent term of 20 years, the "effective" term (from market entry to patent expiration) is somewhere between eight and 10 years (Section 4.2). The study then develops a cost scenario for this biopharmaceutical using representative data from international sources. The scenario suggests that a two-year regulatory delay will reduce a biotechnology firm's rate of return (ROR) by over 5 percent. A one-year regulatory delay would delay the ROR by almost 3 percent.

Regulatory delays were shown to have the most negative impacts on a company's ROR and were of even greater importance than price decreases, production costs or R&D increases. Given current reports of 33-month averages for Canadian health care product approvals, the study showed that reducing this figure to six months could lead to dramatic improvements in a biotechnology firm's profitability (Section 4.3).

The study also analyzes the characteristics and problems associated with various institutional arrangements available to Canadian biotechnology firms including university–industry agreements, strategic alliances and investment capital (via private placements and initial public offerings) (Section 4.4). It also examines the importance of Canadian standards of IP protection and regulation in these institutional arrangements in relation to other factors affecting commercialization of biotechnology products (Section 4.5).

The study examines R&D spending by government, the entire Canadian biotechnology community and top pharmaceutical and biotechnology firms. Canadian government spending for biotechnology (estimated at $272.1 million in 1991-92) is around 4.5 percent of equivalent U.S. federal government biotechnology expenditures (US$4.3 billion). Comparison would suggest more than a *twofold increase* in Canadian governmental support to achieve parity with the U.S. government's biotechnology spending. The comparison shows that the United States supports its biotechnology industry more intensively than does Canada.

Nevertheless, aggregate Canadian R&D expenditures for biotechnology have been growing at a phenomenal 41 percent per year between 1989 and 1993 and reached $991 million in 1993 (or about 47 percent of sales). These R&D expenditure levels are a necessary

prerequisite for the development of high-value biotechnology products. A review of R&D spending by the 26 leading Canadian pharmaceutical and health care firms in 1993 showed that multinationals accounted for 79.9 percent of the total, NBFs for another 10.3 percent and Canada's two leading generic drug firms for the remaining 9.9 percent. Among the multinationals, Merck Frosst and Connaught Lab. ranked first and second respectively. Among NBFs, Allelix, Biochem Pharma, Biomira, Quadra Logic Technologies and Hemosol ranked 17th, 18th, 20th, 21st and 26th respectively. The generics, Apotex and Novopharm, ranked third and 10th respectively (Section 4.6).

Chapter 4 ends with an exploration of key global trends affecting the commercialization of health care biotechnology products and looks at several issues, including the importance of health care reforms (and growing price pressures), vertical integration by multinationals (through mergers with health management organizations), pharmacoeconomics, rising R&D costs and responses in the form of novel product development methods, the growth of strategic alliances and the effects of price controls across the European Community (EC) on pharmaceutical pricing (Section 4.7).

Environmental Regulations and Biotechnology

Chapter 5 examines proposed CEPA environmental regulations for biotechnology products by reviewing current precautionary practices of Canadian environmental NBFs, their costs and any potential for problems. Then, comparable regulations in the United States, Europe and Japan are examined in relation to Canadian proposals. Last, a sketch of environmental biotechnology-related subsidies and programs is provided.

The study found that control measures governing safe practice in the laboratory probably increase total lab costs from 10 percent to 20 percent. For instance, in pilot and full-scale operations for the biotreatment of wastewater, employees normally undergo the precautionary measure of vaccination, wear suitable protective clothing and practise very good hygiene. Treated wastewater is often disinfected (with chlorine or an alternative). These and other health and safety practices raise costs anywhere from 5 percent to 20 percent.

For the bioremediation of soils and sludges in field trials and full-scale operations, all work to date has been done with indigenous naturally occurring microorganisms (NOMs). Regular measurement of total microbial counts during remediaton is the only monitoring. Where necessary, workers wear suitable clothing including respirators. Other precautions (e.g., buffer zones or spraying only when there is no wind) are observed. These measures raise costs from 5 percent to 10 percent. With these sensible environmental precautions in place, the segment of the Canadian bioremediation industry using NOMs has not expressed much concern about issues of environmental safety and human health.

Control measures depend on the type of organism and its level of novelty. The more novel the organism, the more containment will be required, and the higher will be the associated costs. There is, however, no trend in the Canadian environmental biotechnology sector

toward the use of genetically engineered microorganisms (GEMs). In the absence of a compulsory regulatory regime, how informed is the user about pathogenic risk? When literature and data-base searches reveal that an organism (or its progeny) under research investigation is a possible pathogen (either to humans or to the environment), the line of research is stopped by some firms reportedly because of risk from general product liability and risk to workers. This "libel" chill has sensitized a portion of the research community to the point where some strategic decisions are made more on the basis of perceived risk than on perceived opportunity (and scientifically determined risk).

Interviews with the environmental biotechnology stakeholder community have led to some conclusions.

- Microbiological expertise in a firm's project team is an essential ingredient of final success in any bioremediation undertaking as measured in terms of health, environmental safety and efficacy.

- An informed user of environmental biotechnology goods and services is still the best guarantee of a salutary outcome.

- Uninformed use of these products and services is creating market resistance to environmental biotechnologies in some parts of the country.

- Environmentally less-favourable approaches (e.g., dig and haul) continue to underprice bioremediation technologies.

This last point underscores a situation still not adequately addressed by environmental legislation (too little "market pull"). Of great importance in this regard is the absence of stringent environmental liability rules comparable to those established in the United States especially under the *Comprehensive Environmental Response, Compensation and Liability Act* (CERCLA) of 1980, amended by the *Superfund Amendments and Reauthorization Act* of 1986. This legislation establishes an environmental liability regime that is retrospective, absolute and joint and several. (A party can be held liable for past contamination whether the polluting activity was regulated or unregulated and whether the contamination was in compliance or not. Joint and several refers to a situation where one party may be held responsible for all the remediation costs, regardless of the party's contribution to the damage.) No comparable environmental liability legislation exists in Canada at the federal or provincial level. In addition, a lack of public acceptance of biotechnology in general and a fear of liability have dampened scientific endeavour and development in this field.

The study reports documented evidence underlining the need for vigilance and regulatory extension to NOMs. This evidence consists of minimum estimates produced by the U.S. Office of Technology Assessment of numbers of non-indigenous species introduced into that country and the resulting real and potential economic losses. It also consists of reported problems arising from the routine operation of sewage treatment plants (STPs). These include Ontario data (from the Municipal/ Industrial Strategy for Abatement program and

from the Ontario Auditor General) from the International Joint Commission and from the United States. A 1993 outbreak of illness and several reported deaths from the presence of a microbial pathogen in Milwaukee's drinking water raise more serious concerns about the safe operations of STPs and the presence of harmful substances in industrial discharges. These concerns provide ample justification for the extension of the CEPA biotechnology regulations to cover applications involving both NOMs and GEMs.

The study examined comparable environmental biotechnology regulations in the United States, Europe and Japan and found disparities with U.S. regulations which several industry spokespersons argue could lead to competitive disadvantages for Canadian firms. These are driven, in part, by the inclusion of NOMs in the regulations. No government, other than Canada's, regulates or proposes to regulate NOMs within its environmental biotechnology regulations. However, the study demonstrates the need (as outlined above) to protect the environment and human health by extending the regulations to include NOMs. In addition, the Harvard University economist Michael Porter has argued that there is a positive impact from well-designed regulations on competitiveness. The point is that strong standards, in addition to protecting human health and the environment, require the development of high-quality products. Products meeting standards which are internationally recognized as high are less likely to have difficulty entering export markets. Industry's viewpoint is further weakened by the fact that Canadian environmental biotechnology firms lack the industry associations or other organizations to implement voluntary standards.

An industry spokesperson noted that CEPA regulations require additional proof of product safety with changes in habitat, whereas U.S. regulations accept scientific evidence of safety in one habitat as applicable to all continental ecosystems (including Canada). A Canadian regulator responded with the view that health and safety assurances must predominate in the absence of scientific proof that the continent is one territory with respect to any given NOM or GEM. The proposed biotechnology regulation does permit notification for use in all of Canada (Schedule 14). The habitat-specific schedules were intended to provide for reduced and more specific information requirements where appropriate. Biotechnology products regulated under CEPA are frequently living organisms and, therefore, biologically interactive with the receiving environment. Consequently, detailed knowledge of the specific features and structure of the receiving environment must be known in order to develop a reasonable understanding of the likely environmental effects and fate of the organism in question.

During a telephone interview, two U.S. officials characterized Canadian regulations as zero risk based. The regulatory counterpart in the United States, based on the *Toxic Substances Control Act* (TSCA), seeks to balance risks to workers against benefits to society. Some Canadian stakeholders take the opposing view. They contend that the science related to the evaluation of the environmental effects of introduced microorganisms is very much at a developmental stage. In this context, the precautionary approach taken by Environment Canada and Health Canada is prudent and fully justified. They disagree with the suggestion that the CEPA is a zero risk statute. The notification regulation is concerned with the determination of toxicity (i.e., the identification and characterization of potential risk — which is allowed to be higher than zero without a declaration of toxicity). Some level of

evidence of harm or potential harm is required before a product can be declared "toxic." The risk–benefit approach adopted under the TSCA is not mandated under the CEPA. In the opinion of some Canadian stakeholders, the TSCA approach is deeply flawed and, in the present context, would place public health and the environment at considerable risk for the benefit of a single industrial sector.

In the European Union (EU), there is no legislation specific to bioremediation (i.e., the use of microorganisms to clean up the environment). The EU does, of course, regulate GEMs. Country-specific legislation on environmental biotechnology is still in the process of development. There is considerable conflict between the European Commission's initiatives to reduce biotechnology regulation and the direction the European Parliament (EP) wishes to take. As a result, the legal vacuum concerning many IP and regulatory issues in European biotechnology continues.

Chapter 5 also reviews U.S. environmental legislation controlling biology-based waste treatment, differing practices among EC countries, new legislative initiatives in Canadian provinces and environmental biotechnology-related subsidies and programs (Section 5.5).

To conclude the discussion on the proposed CEPA biotechnology regulations, several factors are identified as key issues in the future development of the environmental biotechnology sector.

- Some groups argue that the most significant barrier to the development of the Canadian environmental remediation sector is the lack of clear decision-making processes and liability rules regarding the remediation of contaminated sites in Canada.

- The failure to establish effective means of financing the remediation of "orphaned" sites is also a major problem.

- The NBS of 1981 identified five strategic areas for federal government support including the pollution control and waste treatment sector. All sectors started with equal footing in terms of opportunities provided for them under the strategy and in terms of gaining access to NBS research funds and having the same degree of federal support. This sector's failure to get out of the starting blocks quickly can be attributed to any number of factors: institutional inertia (both government and private sector), perceived low market glamour of the products in the international market place, the diffuse geographical locations of industrial activities in these areas and the lack of an industrial association/national lobby.

In comparison to the above-mentioned issues, the impact of the proposed CEPA regulations seems likely to be marginal. Indeed, if these broader policy questions are resolved, the market for firms capable of providing safe and effective environmental remediation technologies is likely to be extremely favourable.

Intellectual Property Rights

Chapter 6 explores the economic impact of current levels of IP protection for biotechnology inventions on the ability of Canadian biotechnology firms to finance R&D and to gain access to foreign technology. Where possible, the study identifies Canada's interests in this policy area and provides advice on optimal Canadian strategies for IP protection in the light of both industry and consumer interests. Research was based on interviews (with IP practitioners, industry representatives, technology transfer officials in universities and research institutes, and consumer spokespersons) as well as on a review of pertinent literature.

Despite the fact that the United States and Europe have been applying the principles of patent law to biotechnological inventions for almost two decades, law governing IP rights remains unclear in many respects. In all jurisdictions, policy makers have been faced with controversial issues, either in the application of the law itself or in the implementation of policy decisions intended to adapt patent law to this new, important technology. Some of the most compelling controversies concern the extension of patents to genetic material and lifeforms, including cell lines, plants, animals and human body parts. Other concerns have focused on issues relating to the scope of patent protection granted to biotechnological material and to economic rights such as exemptions for researchers and farmers. To date, neither governments, the courts nor patent offices have been able to settle completely the legal uncertainty surrounding the protection of biotechnological inventions.

The study also reviews the nature of patents including the four basic requirements for patentability: novelty, non-obviousness, practical utility (or industrial applicability) and the specification which discloses the invention. The scope and types of protection allowed in claims are also discussed. The study reviews plant breeders' rights and recent developments in those rights as a result of revisions to the International Convention for the Protection of New Varieties of Plants (UPOV).

International aspects of IP protection are examined, including World Intellectual Property Organization (WIPO) treaties, such as the Paris Convention of 1883, the European Patent Convention (EPC) of 1973, and existing IP legislation and current legislative initiatives in the United States, Europe and Canada. The study examines the compromise biotechnology patenting directive of the European Union (EU) which was recently rejected by the European Parliament. The directive was an effort to provide a uniform approach throughout the EU toward patenting genetically altered organisms and other biotechnological inventions.

The study also examines other important patenting issues affecting biotechnology inventions in Canada including compulsory licensing of pharmaceuticals, patenting higher lifeforms and the deposit of biological material to satisfy disclosure requirements.

A review of Canadian biotechnology patent data and statistics (Section 6.2) revealed a significant decline in Canadian biotechnology patent applications since the peak of about 2,350 applications in 1989. The decline was dramatic in 1992 and 1993 and has been

unexplainable either by the Canadian Intellectual Property Office (CIPO) or by the Intellectual Property Policy Directorate (IPPD) in Industry Canada.

An analysis of summary CIPO statistics found that the applicant countries for biotechnology patent applications filed in Canada were (in order) United States, 49 percent; Japan, 13 percent; Germany, 8 percent; United Kingdom, 6 percent; France, 5 percent; Switzerland, 4 percent; and Canada, 3 percent. Of this sample of 3,220 laid-open applications, 16 countries had more priority applications than did Canada. (The priority country is the country of first filing of a patent application.) These countries were (in order) the United States, 54 percent; Japan, 13 percent; United Kingdom, 7 percent; Germany, 7 percent; France, 4 percent; Switzerland, 1.5 percent; Italy, 1.2 percent; and Australia, 1 percent. Canada had only two priority applications. The data indicate that most applicants, with the exception of Canadian, and possibly Dutch applicants, file first in their home countries. Most multinationals file first in their home country.

The value of IP protection derives from the size of (and access to) the market in which that protection exists. The markets in order of preference for Canadian NBFs is, therefore, the United States first, Europe second and either Japan or Canada third. Since all but 3 percent of Canadian biotechnology patent applications come from foreign inventors (and 94 percent of North American applications come from the United States), most Canadian IP practitioners prosecuting patent applications in this country represent applicants residing in the United States. These data suggest that strengthening biotechnology IP protection in this country may have significant economic impacts and could lead to an acceleration in the growth of Canada's biotechnology trade deficit.

Analysis of patent data showed that the top 10 biotechnology patent applicants (i.e., firms) in Canada filed 530 applications (16 percent of the total). Four were based in the United States; two each were from Germany and Switzerland; and there was one each from Japan and the Netherlands. Although biotechnology patenting is not concentrated among a few firms, the profile of the leading biotechnology patent applicants in Canada further demonstrates the competitive advantage of the American, Japanese and European biotechnology industries. The analysis also shows that Canadians not only lag behind in the overall number of patent applications but also in the number of patents filed per Canadian biotechnology applicant.

When analyzed by type of applicant, the patent data base showed that U.S. companies file proportionately more than other U.S. applicants (61 percent of all examined U.S. applications). This holds for Canadian companies but much less so (31 percent of all examined Canadian applications). The data also show that the rate of filing by Canadian companies is about one third of their U.S. counterparts. An explanation may be that U.S. companies are better capitalized than their Canadian counterparts or that U.S. firms are at a more advanced stage of development. It may also be that the previously reported finding of chronic underfinancing for Canadian firms contributes to their inferior development vis-à-vis U.S. firms.

In Section 6.2, survey results on IP issues in the Canadian biotechnology community identify the various methods used to protect intellectual property during the last five years.

- Large firms (more than 100 employees) used patents more than trade secrets or other methods to protect their IP between 1989 and 1993.
- Smaller firms used trade secrets more than patents to accomplish the same goal.
- Large firms (and small firms with 11 to 25 employees) reported that patents provided more effective IP protection than did other forms of IP protection.
- Trade secrets ranked first in effectiveness for very small (one to 10 persons) and intermediate (26 to 100 persons) Canadian biotechnology firms.

Section 6.3 examines a number of current IP issues identified during interviews or from supplementary research. Because health care dominates commercialization and sales activity in biotechnology at this point, most Canadian IP practitioners serve the health care sector. Consequently, for these professionals, IP issues focus on this sector, in general, and pharmaceutical products, in particular. The views of Canadian health care biotechnology companies depend on whether the company is a small NBF, large multinational or a Canadian generic drug company. Canadian NBFs tend to divide between those seeking concessions from the government to nurture development of the domestic industry and those seeking a "level playing field" or harmonization with perceived global standards in efforts to gain access to global markets. However, when it comes to biotechnologically derived drugs, there is some congruence between the views of Canadian NBFs and generic drug companies.

Canadian IP practitioners usually represent either large multinationals or Canadian generic drug companies, but never both. In some instances, they will represent NBFs and either large multinationals or generic drug companies. However, established corporations (i.e., the large multinationals) overwhelmingly dominate the business (and hence the views) of the IP practitioner community which is based primarily in central Canada. For this reason, the views of Canadian IP practitioners are dominated by the domestic commercialization issues multinationals are facing rather than by global IP strategies. The IP practitioner interviews in the study reflect this reality. To the extent possible, the study attempts to redress this imbalance with supplementary research.

The economic issue of foreign ownership of the IP derived from R&D investments in Canada was examined. The country of residence of the owner is pertinent to the location of subsequent investments to develop and manufacture the underlying technology. The Patented Medicine Prices Review Board (PMPRB) reported total R&D expenditures of $503.5 million in 1993 by 70 reporting companies with active Canadian patents pertaining to a medicine sold in Canada. These companies were primarily foreign multinational pharmaceutical and biotechnology firms. The issue can be framed as follows: how much of this total R&D expenditure was spent on discovery research leading to IP owned by

Canadians? Only the university/hospital component of these R&D expenditures may give rise to Canadian IP ownership rights and, in this case, IP ownership of the R&D expenditures are often retained by the foreign company investing in these public research institutes. Hence, the question arises as to the long-term, value-added economic significance of these R&D investments for Canada.

The study explores strategies used by Canadian research institutions to retain IP ownership of industry-sponsored R&D. It also identifies, in at least one major Canadian university (and probably others), a spectrum of arrangements concerning IP ownership of industry-sponsored research. Concerns at this institution revolve on the question of ownership of the research, (i.e., the student, professor, university, general public or industry) and extend to the freedom of staff and students to conduct independent research. Concerned university staff are now drafting ethical guidelines in an attempt to address these issues.

The study reviews global patent strategies from the perspectives of both firms and governments. These perspectives are in constant flux as firms adapt to developments in domestic and international legislation and regulation. The study clarifies differences in the Canadian and U.S. patent systems for resolving disputes concerning IP ownership of the same invention. It also discusses differences in the one-year grace period allowed by both countries for disclosure of an invention and the use of this grace period by academic scientists for scholarly pursuits. The importance of the priority date is clarified for filing patent applications for a particular claim (or set of claims) internationally. It also notes the recent change toward harmonization in the U.S. patent system to a 20-year patent term, based on the date of filing of an application, and the existence of a provision under U.S. patent law for patent term restoration for reasons related to prolonged regulatory review and the like.

As well, the study examines a number of global patent issues identified during interviews and the comparative advantages that result. These include:

- strategies for the development of "follow-on" products of drugs by originator firms using U.S. law and court precedents to lock out competitors;

- obtaining the broadest possible claims to biotechnology inventions in patents in important markets (a phenomenon called "broad blocking patents");

- aggressively defending patents and suing others for patent infringement;

- deferral of examination of Canadian patent applications as a deterrent to Canadian innovators;

- dedicating patents for patented medicines to the public in Canada after establishing market share to circumvent the jurisdiction of the PMPRB; and

- the prohibition of drug manufacture for export purposes during the period when a patent has expired in a foreign country (e.g., the United States) but

is still valid in Canada.

Economic issues related to the debate on pursuing a strategy of international harmonization versus the nurturing of Canadian biotechnology are reviewed. This is followed by an examination of legal issues relating to the subject matter and scope of biotechnology inventions. The topics covered include the patentability of higher lifeforms, plant breeders' rights, broad blocking patents, uncertainty of patent scope, the opposition process to challenge issued patents, process-based patents and deposits of biological material. Other legal issues are grouped under the heading of "effective patent term" and cover CIPO delays in reviewing patent applications and other policy issues, patent filing first in other countries, erosion of an effective patent term, compulsory licensing, and the PMPRB and patent dedication issue.

The main Canadian patent policy areas which were raised in interviews included broad blocking patents, compulsory licensing of pharmaceuticals and section 55.2 (the patent notice of compliance link).

A leading Canadian new biotechnology firm (NBF) spokesperson suggested an "opposition" appeal process at the CIPO for challenging applications for broad blocking patents within some review period (e.g., nine months) and at small cost. This would afford smaller NBFs, with competing but more specific technologies, the opportunity to object to broad blocking patents of large multinationals in an expeditious and relatively inexpensive way. This appeal mechanism exists now in the European Patent Office.

Both the generic drug industry and consumer spokespersons argued for the return of compulsory licensing of pharmaceuticals while representatives of multinational corporations were opposed. Some Canadian NBF representatives, however, were pleased with the abolition of compulsory licensing since they attributed increased R&D investments in Canada to the Bill C-91 amendments to the *Patent Act*. Under the General Agreement on Tariffs and Trade–Trade-Related Intellectual Property (GATT–TRIP) agreements and North American Free Trade Agreement (NAFTA) international treaty obligations, Canada cannot reinstate compulsory licensing of pharmaceuticals. In addition, there are broader trade and industrial policy issues at stake which would be jeopardized with the return of compulsory licensing.

The Bill C-91 amendments set up another issue (referred to in the text as the "section 55.2 issue") which has led to the blocking of over 50 applications for approval to market generic drugs in Canada. A generic drug industry spokesperson argued that these court challenges, if left unchecked, will delay, for frivolous reasons, Canadian market entry of these generic drug products for years and will lead to sales losses for the companies and to increased costs by Canadian purchasers (including provincial formularies) of pharmaceutical products. Although it is unlikely that generic biopharmaceutical products have been caught in this litigious net at this point, this issue may have ramifications for Canadian NBFs commercializing therapeutically and biochemically similar (i.e., "me too") biotech products or biotech products using different processes. Under section 55.2, these products may be

challenged by owners of broad blocking patents.

Section 6.3 of the study concludes with a look at sources of uncertainty in the United States surrounding the application of patent laws to biotechnology, and a detailed examination of the U.S. Orphan Drug Law and the comparative advantages it has provided U.S. NBFs.

Section 6.4 looks at optimal strategies for IP protection to encourage significant growth in Canadian biotechnology start-ups and to attract sizable foreign investments in R&D and manufacturing. An attempt is made to identify any constraints which may affect the pursuit of these objectives, while ensuring wide availability of new products and technologies at competitive prices. Given the wide range of objectives, this is a formidable task. However, the requirement contained in the *Patent Act Amendments Act, 1992* for a 1997 review of its provisions provides a vehicle whereby recommendations could be discussed and evaluated over the next two years. The 1997 policy review and debate is anticipated to yield a set of options for the Minister's consideration.

The recommendations are based primarily on the survey results, stakeholder interviews and the findings discussed in Section 6.3 under current IP issues. The current IP and investment climate for biotechnology in this country has resulted in both the Canadian generic drug industry and health care NBFs facing similar roadblocks to their development. Generic drug companies are making off-shore investment decisions for manufacturing activity which represent lost jobs and opportunities for Canada. Health care NBFs are cash strapped and are actively seeking strategic alliances with foreign multinationals to continue their commercialization activities. If current trends continue, this sector faces the prospect of being taken over by foreign multinational enterprises.

Are there legislative inducements within Canada's IP laws, policies and regulations which could tip the economic balance sufficiently to achieve several highly desirable economic, social and cultural goals? These goals could be defined as follows.

1. To ensure continued competitive pricing for medicines in this country.

2. To reduce Canada's growing pharmaceutical trade deficit.

3. To improve access to capital for Canadian health care biotechnology firms' product development.

4. To increase Canadian biotechnology R&D and manufacturing investments.

5. To reduce Canada's growing trade deficit in the health care biotechnology sector.

6. To obtain (and retain) Canadian IP ownership of its biotechnology research.

To meet these goals, the study proposes an approach first suggested by the economist, Paul Romer.[2] It involves establishing an industry investment board as an institutional arrangement that could provide more financial support for innovative activity and direct it toward areas with large economic payoffs. The aim would be to create an independent source of funds for commercially relevant biotechnology research that would be under the control of people in the biotechnology private sector who are knowledgeable about the opportunities. Romer's approach has a salutary effect on the threat to academic freedom posed by industry-sponsored biotechnology research.

The study outlines Romer's economic rationale, and situates Canadian biotechnology inventions as non-rival economic goods (i.e., economic goods for which consumers are not rivals, once they are produced). Non-rival goods include intellectual property such as biotechnology patents and trade secrets. Romer notes that the production of non-rival goods makes economic growth possible.

Romer identifies two distinct problems in providing non-rival goods: how to share costs and how to select the most promising opportunities for investment. People will normally choose to be free riders if they can. They will not share the fixed costs of goods that are freely disseminated if they do not have to. Also, assembling all the information necessary to decide which of the extremely large number of possible non-rival goods to produce is very difficult. The government's power of coercion makes it uniquely capable of solving the cost-sharing problem. However, governments have also wasted resources on non-optimal strategies. Markets can solve the sharing problem only by introducing monopoly distortions, but they are better than governments at selecting the opportunities to pursue and avoiding wasteful spending.

Because people operating in the market are motivated by the potential for profit, they seek out only those non-rival goods that have real value. The parallel or simultaneous search by large numbers of market participants can efficiently evaluate many possibilities. Bankruptcy constraints quickly cut off the flow of resources to projects that turn out to be unpromising.

Under existing institutional arrangements for producing non-rival goods, one or the other of these extreme mechanisms is typically selected as being most appropriate for a given type of good. In the public good portion of the non-rival goods' continuum, the government pays for basic research and gives away the result. (Romer cites the example of the polio vaccine). At the other end of the continuum, society relies on market mechanisms to make investment decisions and accepts the limits on dissemination and the monopoly distortions that the use of the market entails.

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[2] Romer, P.M. *Implementing a national technology strategy with self-organizing industry investment boards.* Brookings Papers: Microeconomics 2, 1993, pp. 345-399.

The existing arrangement with government provision of basic research and market provision of final goods seems to work reasonably well for non-rival goods at the extreme ends of the continuum. It is the intermediate zone where the most important opportunities may be missed. This area may offer particularly large returns from investment in research. The Canadian biotechnology community would seem to be currently situated in the intermediate zone. Romer's proposal mixes government and private sector mechanisms in such a way as to combine government's efficiency at solving free-rider problems with the market's effectiveness in selecting practical problems that offer the highest rates of return. Market participants can then make the right decisions about where the returns on investment are highest for the industry.

In adapting Romer's model, the Minister of Industry could determine that collective action was necessary to address the Canadian health care biotechnology community's goals (as listed above), since independent action by individual firms would be ineffectual. This collective action could begin with a white paper identifying the industry-specific public good. The Minister could hold hearings to ensure that collective action did indeed address a genuine public need. The paper could specify a levy to be applied in the form of a tax on pharmaceutical sales. This tax initiative would be backed by the full force of law and imposed on the entire sector. The proceeds, however, would not go to the government. Instead, as Romer indicates, the plan would be to create an investment board [call it the "Canadian Health Care Biotechnology Development Board" (CHCBDB)] that would fund a full range of worthwhile projects such as university-based research projects in biotechnology and the development of biotechnology manufacturing capability.

The CHCBDB would have a board of directors drawn from the government and the Canadian biotechnology community and would operate as a quasi-private, non-profit foundation. The board would be limited by the terms of enabling legislation, as proposed in the white paper, but would otherwise have wide latitude to make decisions and would operate at arm's length from the political level of government. A general limitation would require the board to invest only in common property resources that benefit the entire community. For example, a specialized manufacturing capability (viz., fermentation machinery) would be made available (for sale or lease) to all Canadian health care biotechnology firms on equal terms. Funded university research would be owned by the resident university but could be licensed to all Canadian health care biotechnology firms on equal terms.

Romer notes that the enabling legislation should also specify that absolutely no board funds could be used to support lobbying, public relations or any kind of political activity. Nor would direct or indirect kickbacks or side payments to firms in the industry be permitted. He suggests a tax rate of less than 2 percent. At 1 percent to 2 percent of pharmaceutical sales, this would amount to some $100 million to $200 million in funding per year (depending on whether prescription and over-the-counter medicines are included). He also notes that the legislation should articulate the general principle that the tax is a domestic consumption tax rather than a production tax. Units produced domestically for sale abroad would not be subject to the tax, but units produced abroad and sold domestically would. The legislation would also mandate equal treatment for all members of the community.

This rationale leads to the following recommendation.

> ***Recommendation 1:*** *That the Minister of Industry introduce a white paper to address the public good as identified in the Canadian health care biotechnology community's goals (listed above). The Minister could hold hearings to ensure that the collective action called for in the white paper did indeed address a genuine public need. The paper could propose a levy in the form of a tax on domestic pharmaceutical sales. This tax initiative would be backed by the full force of law and imposed on the entire sector. The proceeds, however, would not go to the government but would, instead, be used to create an investment board [called the "Canadian Health Care Biotechnology Development Board" (CHCBDB)] that would fund a full range of worthwhile health care biotechnology projects, including university-based research and the development of biotechnology manufacturing capability.*
>
> *The CHCBDB would have a board of directors drawn both from the government and the Canadian biotechnology community and would operate as a quasi-private, non-profit foundation. The board would be limited by the terms of the enabling legislation but would otherwise have wide latitude to make decisions and would operate at arm's length from the political level of government. A general limitation would require the board to invest only in common property resources that benefit the entire industry.*
>
> *The enabling legislation should also specify that absolutely no board funds could be used to support lobbying, public relations or any kind of political activity. Nor would direct or indirect kickbacks or side payments to firms in the industry be permitted. A suggested tax rate of 1 percent to 2 percent of pharmaceutical sales would generate some $100 million to $200 million in funding per year (depending on whether prescription and over-the-counter medicines are included). The legislation should articulate the general principle that the tax is a domestic consumption tax rather than a production tax. Units produced domestically for sale abroad would not be subject to the tax, but units produced abroad and sold domestically would. The legislation would also mandate equal treatment for all members of the Canadian biotechnology community.*

In Section 6.3, a number of current IP issues were identified. Prominent among them is the section 55.2 issue which has apparently introduced inequities and inefficiencies into the Canadian pharmaceutical market and increased costs to Canadian consumers. By erecting a barrier to competition on patent expiration, the regulation appears to contradict the intent of the new patent regime established under Bill C-91 amendments to the *Patent Act*. In this respect, the PMPRB has stated that "Bill C-91...established a new regime to facilitate the entry of competitors immediately upon the expiry of a patent, to stockpile and seek regulatory approval of products prior to the expiry of a patent.... These amendments appear to have been designed to ensure patentees enjoy the benefits of their statutory rights during

the normal patent term, but not beyond it."[3] As a result, the study makes the following recommendation.

> ***Recommendation 2:*** *That the section 55.2 amendment to the Regulations of the* Patent Act *(resulting from Bill C-91) be abolished as quickly as possible, and that the Minister of Health's* de facto *injunction be lifted from all relevant cases now before Canadian courts to allow the corresponding applications for regulatory approval for generic drug products to proceed expeditiously to the issuance of their notice of compliance.*

The study raises the issues of broad blocking patents, their dampening effect on innovation and the development of the Canadian biotechnology industry. It also discusses the difficulties associated with a policy allowing a deferral of the examination of a patent application for up to seven years. Abolishing this deferral would intensify the demand for resources at CIPO for patent examination. In some instances, patentees abandon their patents before examination which results in a resource saving for CIPO. As a result, there are trade-offs, and the recommendation below reflects this fact. The study also noted that the European Patent Office has provided one very effective remedy to patent applicants to challenge the existence of such patents and to raise other objections concerning the implications of patent applications. This reasoning led to the following two recommendations.

> ***Recommendation 3:*** *Since broad blocking patents impede the development of Canadian new biotechnology firms, the Canadian Intellectual Property Office should avoid issuing broad blocking patents by determining the subject matter of the invention and should grant claims that cover that subject matter only. This involves assessing whether the subject matter of the invention is really a product (where claims to the product will create barriers to the development of the industry) or a process of manufacturing or use of a product (where claims to the process will provide patent protection but not impede the development of the industry).*
>
> *The period of deferral for examination of patent applications should be reduced from seven years to five years.*
>
> *The Canadian Intellectual Property Office should create written and published policies on the breadth of claims for biotechnology inventions.*

> ***Recommendation 4:*** *That the Minister consider amendments to the* Patent Act *providing for an opposition appeal process at the Canadian Intellectual Property Office similar to that available at the European Patent Office. The process should allow challenges to applications for broad blocking patents within a review period*

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[3] Patented Medicine Prices Review Board. Dedicated Patent - Notice and Comments. PMPRB Bulletin, Issue No. 15, January 1995, pp. 5-8.

(e.g., nine months) and at small cost to the challenger.

The study reviewed briefly some of the advantages accruing to U.S. NBFs seeking to commercialize their biotechnology products under the provisions of the U.S. Orphan Drug Law. The following recommendation seeks to level the playing field on this matter for Canadian NBFs.

> ***Recommendation 5:*** *That the ministers of Industry, Health and other relevant departments should consider passage of a law similar in scope to the U.S. Orphan Drug Law to provide Health Protection Branch assistance to Canadian new biotechnology firm orphan drug developers in protocol design for new drug approval or product licence approval applications, research grants for clinical and preclinical studies of orphan products, specific R&D tax credits and a grant of a period of market exclusivity to the first Canadian new biotechnology firm that receives approval for an orphan drug.*

Interviewees emphasized the critical importance of a pro-active federal government monitoring and negotiating role to mitigate the effects of proposed and enacted legislation of foreign countries on Canadian NBFs. Examples provided during interviews included the U.S. Orphan Drug Law (for which a separate recommendation is provided above) as well as the U.S. "Boucher Bill" and the U.S. reduction to practice legislation. Where proposed or enacted legislation harms Canadian NBFs, the federal government should work with these countries to try to reduce the adverse impact of their legislation. Or it should consider adopting similar practices in Canada. Accordingly, the following recommendation is provided.

> ***Recommendation 6:*** *That the Minister of Industry consider the establishment of a biotechnology advisory body to monitor and advise on the effects of proposed and enacted policies, practices and legislation of foreign countries on Canadian new biotechnology firms. A high priority activity of this body should be to undertake an analysis of protectionist measures and preferential treatment afforded foreign biotechnology companies by their home governments through intellectual property provisions and/or regulatory and other agencies. Where proposed or enacted policies, practices or legislation harm Canadian new biotechnology firms, the federal government should work with these countries to try to reduce their adverse impacts. Failing this, the federal government should consider the adoption of similar Canadian policies, practices and legislation.*

The study also noted that article 4*bis* of the Paris Convention of 1883 allowed for a complete patent term in any particular country of the Union (e.g., Canada) based on the date of filing of the application in that country. This was done despite the apparent inequity set up by the fact that this date might follow the priority date for the patent in some other country of the Union (viz., the United States) by up to 12 months. However, the study

argues on the grounds of economic benefit that there should be no prohibition to manufacture in Canada for export purposes during the time when a patent has expired in another country (e.g., the United States) but is still valid in Canada. By locking Canadian generic drug companies out of this export market, (e.g., the U.S. market during this critical period), American-based multinationals obtain a competitive advantage which they then use to control the generic market for a given pharmaceutical with an expired patent. And with the rise of managed care organizations in the United States, the generic business in that country is growing rapidly. Canadian patent law appears, therefore, to set up a non-tariff trade barrier which works to the disadvantage of this Canadian industry. The following recommendation aims to remove this impediment.

> ***Recommendation 7:*** *That the Minister of Industry or appropriate counterpart consider amendments allowing the manufacture, for export, of pharmaceutical products still under an existing patent in Canada to countries where the corresponding patents have expired.*

The study noted that although NAFTA recognizes patent term extension (paragraph 12 of article 1709), it is not currently available in Canada under the *Patent Act*. Patent term restoration has been implemented in the United States, Europe and Japan. In view of the increased regulation proposed for biotechnology products and processes, Canadian biotechnology firms would benefit from a change to Canada's laws to provide for patent term restoration. Accordingly, the following recommendation is provided.

> ***Recommendation 8:*** *That the Minister of Industry consider amendments to the* Patent Act *to provide for the extension of a patent term in certain appropriate instances (viz., following prolonged regulatory review).*

In conclusion, this study has aimed to provide background economic research and recommendations to promote the support and development of biotechnology policy, legislation and regulation to strengthen and prepare the Canadian biotechnology community to compete in a global marketplace.

CHAPTER 1

OVERVIEW OF THE CANADIAN BIOTECHNOLOGY COMMUNITY

1.1 Introduction

This study was commissioned by the federal government to provide background economic research to support the development of biotechnology policy, legislation and regulations including the National Biotechnology Strategy (NBS), *Patent Act* amendments and the drafting of biotechnology regulations under the *Canadian Environmental Protection Act* (CEPA).

CEPA defines biotechnology as "the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms" [CEPA, section 3 (1)]. To assist and inform the development of the federal government's biotechnology activities, this economic study has adopted the perspective of the public interest. It aims to support initiatives which maximize social welfare in this country. This includes both the value-added contributions of biotechnology to the Canadian economy and its potential to improve the environment and quality of life of Canadians.

The authors acknowledge that some details in the ambitious terms of reference established by the tri-department Scientific Authority could not be fully addressed in this study. In some instances, reliable information does not exist or cannot be accessed (by the government or the authors) or produced within the resource guidelines of the project. In other cases, it was only possible to provide an outline of the issue with the intention of opening up these policy domains for further examination and debate. Readers should also note that this background research report does not necessarily represent the views of the Government of Canada.

1.2 Canada's National Biotechnology Strategy

Biotechnology presents a number of critical and unprecedented policy challenges to the governments of all industrialized societies. The Canadian federal government's response, the National Biotechnology Strategy (NBS), began in 1983. It is administered by two committees: the National Biotechnology Advisory Committee (NBAC) and the Interdepartmental Committee on Biotechnology (ICB). NBAC, with representation from industry, academia and government, advises the Minister of Industry on issues relating to the development of the industry. The ICB, chaired by a senior departmental executive, helps to co-ordinate federal government activity in biotechnology at the assistant deputy minister level and has responsibility for the allocation of NBS funds. An expert,

interdepartmental committee, the Biotechnology Co-ordination Group (BCG), develops policy and funding recommendations to be considered by the ICB.

Despite a reasonably comprehensive plan for biotechnology, a 1988 report[4] by the Organization for Economic Co-operation and Development (OECD) noted that neither the NBAC nor the ICB had sufficient mandate or resources to assume an effective "pro-active" role, given the tremendous strides which would be necessary before Canada could fully reap the opportunities presented by biotechnology. Although the Canadian strategy had identified and promoted priority areas for research, based on the perceived opportunities to strengthen Canada's natural resource industries through biotechnology, the OECD report concluded that funding levels appeared to have been inadequate to build a coherent strategy based on these priorities, to support research programs at universities and government institutes in co-ordination with industrial priority areas, and to ensure industrial involvement in these research programs.

The OECD report went on to identify a need in Canada for greater strategic co-ordination between industrial development and university and government research, and for the resolution of aims, roles and responsibilities within and between federal and provincial governments in relation to biotechnology. The federal government strategy in 1988 hoped to rectify a "fragmented and incoherent" research effort at universities and research institutes in biotechnology by providing the Natural Sciences and Engineering Research Council (NSERC) with greater resources to support strategic projects based on industrial or other priority areas.

The 1991 NBAC report[5] identified seven issues to enhance Canada's international competitiveness in biotechnology through changes in private sector decision making and public policy designed to translate research discoveries into business opportunities.

1. **Financial Resources for Growing Companies:** The lack of equity financing in Canada has inhibited biotechnology commercial development and exposed Canadian companies to takeovers by better-financed foreign competitors.

2. **Human Resources:** The shortfall in highly qualified personnel with managerial, production, research and regulatory skills suggests the need for changes in Canada's education and immigration policies.

3. **Regulations:** Regulatory delays and uncertainties discourage new research and investments in commercial facilities. This drives up the costs of innovation and undermines public confidence.

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[4] Organization for Economic Co-operation and Development. *Biotechnology and the changing role of government.* Paris, 1988.

[5] National Biotechnology Advisory Committee. *National Biotechnology Business Strategy: Capturing Competitive Advantage for Canada.* 5th Report, Industry, Science and Technology Canada, 1991.

4. **Intellectual Property Protection:** The 1991 patent system, i.e., the pre-Bill C-91 environment, caused uncertainty and delay in translating scientific discoveries into commercial successes. The tardiness in developing regulations pursuant to the new *Plant Breeders' Rights Act* also constrained the commercial application of new biotechnologies for use in the agriculture and forest industries. (Note that the passage of Bill C-91 has improved this situation. While some uncertainties remain surrounding the patentability of higher lifeforms, microorganisms can clearly be patented. See Chapter 6 for a more complete discussion.)

5. **Infrastructure for Scientific Research:** The erosion of funding support for infrastructure maintenance and upgrading for university research has meant that, increasingly, Canada is losing its best graduate students to better-equipped foreign facilities and is failing to attract sufficient students to the life sciences.

6. **Public Perception and Market Acceptance:** The introduction of new products of technology necessitates a balance between regulation and promotion, equity and efficiency, protection of the public and environment, as well as the furtherance of private interests and economic growth. The NBAC recognized the importance of the public's perception of risks and benefits associated with specific commercial applications of new biotechnologies to the overall success of this pursuit in Canada, and plans were made to include the general public as an important stakeholder in the deliberations leading to the implementation of the recommendations in its report.

7. **Strong Voice for Industry:** The NBAC supported efforts to develop a strong, credible and respected voice and a supporting infrastructure to play an advocacy role for the biotechnology industry both nationally and internationally.

This study examines the views of Canadian biotechnology stakeholders on the progress achieved in addressing these issues. (See, for example, sections 4.1, 4.4, 4.5, 5.2, 5.3, 6.2 and 6.3 for stakeholder views on specific Canadian biotechnology issues.)

1.3 Definitions and Organizational Relationships in Biotechnology

Broadly construed, biotechnology has been part of civilization since prehistoric times when humankind moved from hunter–gatherer to agrarian societies. The term came into general usage in the late 20th century and is applied to techniques for directly manipulating the genetic code of plants or animals, and to the use of biogenetically engineered microorganisms in the manufacture (or degradation) of materials of economic value. Specifically, "biotechnology" refers either to recombinant deoxyribonucleic acid (rDNA), cell fusion or related technologies, as well as to advanced bioprocess engineering. This variability in the meaning, coupled with the fact that, as a molecular science, the same technology application can and often does diffuse into more than one economic sector, makes precise classification difficult.

Firms from a number of traditional industries have been involved in the commercial development of biotechnology. For instance, applied research using rDNA and cell fusion technology is currently being conducted by firms in the pharmaceutical, chemical, agricultural and energy industries. These technologies are also being exploited by newly established firms that specialize in genetic engineering and cannot be clearly subsumed under Statistics Canada's Standard Industrial Classification. Other firms have been established exclusively to fund biotechnology ventures, and still others have formed to provide necessary equipment and supplies. So it is more accurate to speak of a community of organizations involved in biotechnology than of a biotechnology industry. Freeman and Barley[6] use the term "community" to indicate that these organizations form a whole, held together by commensalistic and symbiotic ties. The community encompasses all public or private organizations that pursue, produce, sponsor, fund or regulate research involving the aforementioned technologies and the products manufactured by processes derived from them.

The Canadian biotechnology community can be thought of as including at least nine categories of organizations.

1. **New Biotechnology Firms (NBFs):** These have been established to pursue applied research and development (R&D) in areas of commercial promise, e.g., Allelix, BioChem Pharma, BioMega, Biomira and Quadra Logic Technologies.

2. **University Departments:** Departments of microbiology and related disciplines are carrying on basic and applied research, e.g., Centre for Plant Biotechnology at the University of Toronto and the Protein Engineering Network of Centres of Excellence (PENCE) at the University of British Columbia.

3. **Research Institutes:** These institutes are partially or fully engaged in biotechnology research, e.g., Ag-West Biotech, Biotechnology Research Institute at the National Research Council, Centre de recherche industrielle du Québec (CRIQ), Centre for Cardiovascular Research at the Toronto General Hospital, Centre for Food and Animal Research and ORTECH.

4. **Established Corporations:** Some companies in the chemical, pharmaceutical, agricultural and other industries have either begun their own biotechnology R&D operations or are involved in strategic alliances with NBFs, university departments or research institutes, e.g., Ortho Biotech and Glaxo Canada.

5. **Venture Capital Firms:** A substantial amount of funding has been provided to NBFs by these companies, e.g., Gordon Capital and Yorkton Securities.

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[6] Freeman, J. and S. Barley. *The strategic analysis of inter-organizational relations in biotechnology.* Chapter 6 in *The strategic management of technological innovation.* Edited by R. Loveridge and M. Pitt. Chichester, England: John Wiley & Sons, 1990.

6. **Regulatory Bodies:** These organizations have jurisdiction over the products and processes of biotechnology research, e.g., Health Canada, Agriculture Canada and Environment Canada.

7. **Industrial Associations:** In some instances, associations have been established to further the aims of this community, e.g., Industrial Biotechnology Association of Canada, B.C. Biotechnology Alliance and the Toronto Biotechnology Initiative.

8. **Scientific Bodies:** These organizations fund conferences, sponsor research and disseminate relevant information, e.g., the National Science and Engineering Research Council (NSERC) and the Medical Research Council (MRC).

9. **Suppliers:** Companies supply equipment and biological reagents for rDNA and cell fusion research or bioprocess engineering.

The "ecological structure" (i.e., network of dynamic relationships) connecting organizations engaged in commercial biotechnology in Canada is evolving in response to global market forces. Legislative and policy proposals under development by the federal government are planned to strengthen the international competitiveness of Canada's biotechnology community by reshaping this ecology. Consequently, it behooves the policy maker to understand why certain arrangements among biotechnology organizations arise.

There are many institutional arrangements for running economic activities ranging from vertically integrated firms [fully integrated pharmaceutical companies (FIPCOs)] to arm's length transactions [sometimes called quasi-firms[7] or virtually integrated pharmaceutical companies (VIPCOs)[8]]. Each of these extremes along the spectrum of organizational forms involves costs and risks. On the one hand, there are the costs of running an organization; on the other, the costs and risks of setting up, running and monitoring an arm's length market transaction.[9]

There are institutional arrangements intermediate between markets and corporate hierarchies. At one extreme, there is an alliance between a prime contractor and a number of independent sub-contractors to carry out a one-shot contract that, typically, is not

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[7] Thorelli, H. "Networks: between markets and hierarchies." *Strategic Management Journal.* Vol. 7, No. 1, 1986, pp. 37-51.

[8] Burrill, G.S. and K.B. Lee Jr. *Biotech 94: Long-Term Value, Short-Term Hurdles.* Ernst & Young's 8th Annual Report on the Biotechnology Industry, Ernst and Young, 1993.

[9] Hutchinson, G.E. *An introduction to population ecology.* New Haven, CT: Yale University Press, 1978; Williamson, O.E. *Markets and Hierarchies.* New York: Free Press, 1975.

renewed when the terms of the contract have been met. Eccles[10] has defined an intermediate arrangement called a quasi-firm as a co-ordinated contracting mode which relates a prime contractor, as principal, and a group of sub-contractors, as agents, in a recurring relationship. The quasi-firm is a network since two or more organizations are involved in a long-term relationship. Each party in the network bears risks relative to its own activity.[11]

In other network forms, such as the various forms of strategic alliances, all members are joint risk takers. In a typical joint venture, two or more firms put complementary assets together in a self-contained organization which produces goods or services of its own. In this case, the competitive success of the joint firm depends, in part, on its own environment and on competitive conditions.

Further along the continuum toward vertical integration and a hierarchical relationship is the mutual organization — a network like the quasi-firm, but one in which the parties are both principals and agents. "Learning to work together" presumably also prevails in this co-contracting mode.[12] The major difference between mutual organizations and quasi-firms lies in risk allocation. If there were a sufficiently large number of potential members in the mutual organization, there would be no need for such a partnership and a less-committing, quasi-firm would do. It is the small number scenario that contributes to the preference for joint risk taking. Moreover, the mutual organization means that there is asset specificity in the transaction: learning to work together and an investment of tangible and intangible assets by all parties. The mutual organization differs from a fully integrated firm because of communication and co-ordination problems between principals and members which try to appropriate the results for their own profit, and because the participating firms only transfer a portion of their assets to the organization.[13]

Under the VIPCO organizational model, American biotechnology companies have reduced the average cost of developing biopharmaceuticals to US$125 million.[14] In contrast, the Pharmaceutical Manufacturers' Association (PMA) has pegged average development costs

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[10] Eccles, R. "Quasi-firms in the construction industry." *Journal of Economic Behaviour and Organization*, Vol. 2, 1982, pp. 335-357

[11] Thorelli, H. "Networks: between markets and hierarchies." *Strategic Management Journal.* Vol. 7, No. 1, 1986, pp. 37-51.

[12] Koenig, C. and R-A. Thiétart. "The mutual organization: a new form of cooperation in a high technology industry." Chapter 7 in *The strategic management of technological innovation.* Edited by R. Loveridge and M. Pitt. Chichester, England: John Wiley & Sons, 1990.

[13] Shamel, R.E. and M. Keough. "Trends in biopharmaceutical product development and commercialization." *Genetic Engineering News*, Vol. 14, No. 1, January 1, 1994, pp. 6-8.

[14] Burrill, G.S. and K.B. Lee Jr. *Biotech 94: Long-Term Value, Short-Term Hurdles.* Ernst & Young's 8th Annual Report on the Biotechnology Industry, Ernst and Young, 1993.

for its predominantly FIPCO members at $231 million.[15] The widely differing estimates can be attributed, in large part, to risk and its perception. The VIPCO model is inherently a higher risk model since it involves alliances with partners that expose the company to the greater possibility of business failure and to more market scrutiny. Negative results in clinical trials can and have precipitated significant declines in market valuations not only for individual companies but also for the whole industry. FIPCOs are insulated from product failures by virtue of their broader portfolio of investments and revenues as well as the internalization of their business activities. Both features reduce risk and the market's perception of risk but raise product development costs.

Because the early phases of biotechnology product life cycles are typically protracted, only the oldest NBFs have shown more than trivial returns on sales. During the early 1980s, venture capitalists were the primary source of funding for biotechnology start-ups in return for a significant proportion of a firm's equity. Since then, the high costs of R&D, clinical trials and marketing have, in most cases, exceeded the amount of venture capital available to biotechnology firms. Compounding the problem, the amount of available venture capital has actually declined. Most NBFs have been unable to obtain debt financing since they lack sufficient collateral. Consequently, NBFs have been forced to finance their R&D by establishing ties to other organizations with commercial interests in biotechnology.

According to the U.S. Office of Technology Assessment (USOTA),[16] biotechnology's reliance on contract research is without parallel in any commercial area except perhaps for small defence contractors. Joint ventures as well as research, licensing, manufacturing, marketing and product development agreements between NBFs and established firms have also been prevalent. Under the typical R&D licensing agreement, an established firm funds an NBF's development of a product and acquires the exclusive licence to market the product, while the NBF retains the patent rights. The R&D-limited partnership is the most recent trend in financing commercial biotechnology: The NBF usually assumes the role of general partner and hence, all liability. The limited partners buy a share of the NBF's future profits or losses. Investors may be corporations, pension funds, mutual funds or private individuals. The limited partners provide funding in return for equity in a specific product or product line. Unlike other forms of equity financing, limited partners do not participate in the management of the firm by sitting on the firm's board or voting as stockholders.

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[15] Shamel, R.E. and M. Keough. "Trends in biopharmaceutical product development and commercialization." *Genetic Engineering News*, Vol. 14, No. 1, January 1, 1994, pp. 6-8.

[16] Office of Technology Assessment. *Commercial biotechnology: an international analysis.* Washington, DC: U.S. Government Printing Office, 1984.

1.4 Economic Characteristics of the Canadian Biotechnology Community

1.4.1 Survey Methods

The Canadian biotechnology community was surveyed to obtain reliable estimates of its economic performance and overall contributions to the Canadian economy. The survey extended across a larger universe of biotech companies than previous studies had, reached a larger sample of this universe and deployed certain methodological refinements to overcome inherent definitional problems associated with biotechnology. It also provided a vehicle for the expression of views by industry spokespersons on opportunities for, and barriers to, optimal performance by an industry seeking to become more competitive in the global biotechnology marketplace.

The survey universe included all Canadian biotechnology firms currently deploying, or with the potential to deploy in the near to mid-term future, second generation biotechnology. Second generation biotechnology includes rDNA technologies as well as applications using process technology, chemistry and classical engineering. In the environmental domain, bioreactor design and the use of immobilized cells are examples of the newer technologies which have been developed in parallel to genetic engineering. In casting the net more widely, the survey also included environmental firms whose activities fall within the purview of the draft Canadian environmental regulation for imported or manufactured biotechnology products since this regulation encompasses applications deploying naturally occurring microorganisms (NOMs) as well as genetically engineered or modified microorganisms (GEMs).

It is difficult to classify a biotechnology firm's business activity because the underlying technologies diffuse into diverse economic areas. Two examples from our study illustrate the problem. A spokesperson for a large American-based agricultural firm has allocated his company's biotechnology business activity across seven different economic sectors: agriculture, aquaculture, environment, food and beverage, forestry, health care and horticulture. Conversely, a small Vancouver-based company, with a proprietary technology deploying transgenic fish to monitor for the presence of carcinogenic substances, classifies itself as an aquaculture firm but allocates its business into the environmental and health care sectors.

To overcome these classification problems, survey respondents allocated shares of their firm's R&D, and production and sales activities into one or more of 10 broad economic sectors into which biotechnology has diffused:

- agriculture;
- aquaculture including fisheries;
- energy;
- environment;
- food and beverage including fermentation;
- forestry;

- health care including diagnostics, therapeutics and vaccines;
- horticulture;
- mining; and
- pulp and paper.

Respondents also divided their firm's sectoral business according to the type of lifeform (NOM or GEM). They subdivided their company's GEM business in each sector according to its intellectual property characteristics. They were asked to identify how much of their firm's GEM business was based:

- on *innovative* technology, i.e., on ownership of a patented medicine or other proprietary product or technology;

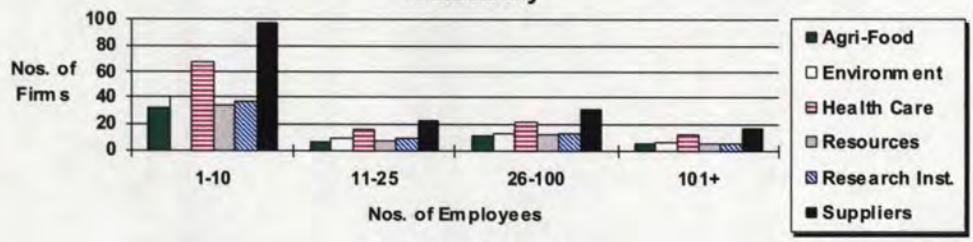
- on *licensed* technology, i.e., on a licensing agreement to make, use or sell a patented product or technology; or

- on *generic* technology, i.e., either a compulsory licence to make, use or sell a patented product or technology (or the freedom to make, use or sell a product or technology whose patent has expired).

Respondents also allocated the sectoral GEM business according to whether the originating lifeform was an *animal* (or its products), a *plant* (or its products) or a *microorganism* (or its products). Last, they divided sectoral activity into two components (microorganisms or their products, and other biotech activity), having first excluded all business activity related to foods, drugs, medical devices and pesticides. The last two requests allowed the development of economic indicators reflecting that portion of the Canadian biotechnology industry likely to be affected by the CEPA biotechnology regulation now under review.

The survey was a stratified random sample of 175 companies from a universe of 538 firms comprising the above definition of the 1993 Canadian biotechnology community. Strata were defined by the number of employees per firm and the activity category in which they were originally classified by publicly and privately assembled directories of the Canadian biotechnology industry. The survey classification scheme is shown in Figure 1.1. Economic analysis was conducted using the sectoral allocation method defined above.

Figure 1.1
Number of Firms by Size in 1993 Canadian Biotechnology Community



The survey involved a series of allocative questions as described above in advance of a 45-to-60 minute telephone interview spanning a detailed set of 60 survey questions. A total of 156 firm spokespersons responded (for a response rate of 89 percent). See footnote 17 for further details.

Table 1.1

Number of Firms in 1993 Canadian Biotechnology Community

Firm Classification	Number of Employees per Firm				
	1-10	11-25	26-100	101+	Total
Agri-Food	33	7	11	6	57
Environment	40	9	14	7	70
Health Care	67	16	21	12	116
Resources	34	8	12	6	60
Research Inst.	37	9	13	6	65
Suppliers	98	23	32	17	170
Totals	**309**	**72**	**103**	**54**	**538**

Note: See foot note[17] for survey details.

As shown in Table 1.1, 538 firms comprised the 1993 Canadian biotechnology industry.

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[17] No private or public Canadian biotechnology data bases contained complete, or even current, information at the firm level. As a result, many such data bases and association membership lists were used to obtain a complete list of 538 Canadian biotechnology firms comprising the universe. The survey was a stratified random sample drawn from this universe. Strata were defined by firm classification and number of employees (as reported in the data bases). Firm classification categories were: agriculture, aquaculture, energy, environment, food and beverage, forestry, health care, horticulture, mining, pulp and paper, research institutes and suppliers.

Since there was a large number of firms with an unknown number of employees, Canada Market Research Ltd. (the surveyors) *oversampled* two categories, large firms and firms with unknown numbers of employees. This procedure provided more reliable data. The derived information on firms with previously unknown size was used to redistribute all such firms among the strata for known size firms in each classification. For instance, the sample results for the unknown size health care firms were used to distribute the total number of these firms among the strata of known size health care firms. This procedure yielded a set of weights based on the ratio of the estimated number of firms to the sampled number in each cell of the universe of firms. A cell was identified by firm classification and number of employees. The weights enabled extrapolation of survey results to the universe of Canadian biotechnology firms. The sample breakdown is provided below.

Most firms were small, having, at most, 10 employees (57 percent) suggesting the industry is still in its early growth stage.

- Among final product manufacturers, there were more health care firms (22 percent), with environmental (13 percent), resource (11 percent) and agri-food (10.5 percent) companies.
- There were also a large number of supplier firms (32 percent), most of which were small as well.
- Research institutes comprised about 12 percent of the industry.

Two thirds of the industry was concentrated in central Canada (Table 1.2). Almost half the health care biotechnology industry (43 percent) was in Ontario, with the remainder clustered in Quebec (24 percent) and British Columbia (16 percent).

Survey Sample Sizes by Sample Categories			
Sample Categories	**Universe**	**Sample**	**Level (%)**
Overall	538	156	29
Size of Firm:			
1-10	309	88	28
11-100	175	54	31
101+	54	14	26
Firm Classification:			
Health care	116	32	28
Agri-food	57	15	26
Environment	70	21	30
Suppliers	170	48	28
Research inst.	65	21	32
Resources	60	19	32

Table 1.2

Distribution of Canadian Biotechnology Firms by Province and Classification in 1993

Firm Classification	Nfld	N.S.	P.E.I	N.B.	Que.	Ont.	Man	Sask	Alta	B.C.	Terr.	Total
Agri-food		2	2	2	12	24	2	2	1	10		**57**
Environment		1		2	17	29	3	2	2	12	2	**70**
Health care	1	2		4	28	50	5	4	3	19		**116**
Resources				2	16	26	2	2	2	10		**60**
Research inst.	1	3		2	14	26	3	2	2	11	1	**65**
Suppliers	1	3	1	6	41	74	7	5	4	28		**170**
Totals	**3**	**11**	**3**	**18**	**128**	**229**	**22**	**17**	**14**	**90**	**3**	**538**
Percentages	**0.6**	**2.0**	**0.6**	**3.3**	**23.8**	**42.6**	**4.1**	**3.2**	**2.6**	**16.7**	**0.6**	**100**

Survey Response Levels by Key Question Categories

Table Ref.	Title	Base Description	Question Ref.	Eligible Sample	Responding Sample
1.7	Empl't. by Sector: 1993	All	Qn.6a-d/ 7a-d	156	142
1.8	Ann. Empl't. by Sector: 89-93	"	Qn.6a-d/ 7a-b	156	142
1.19	Ann. Empl't. by Lifeform & Sector: 89-93	"	Qn.6a-d/7a-b,e	156	91/109/125/139/142[a]
1.9	Sales by Sector: 1993	Firms with Sales Activity	Qn.32a	74	68
1.10	Ann. Sales by Sector:: 89-93	"	Qn.32a	74	29/35/40/49/68[a]
1.11	Sales by Region: 1993	"	Qn.32a/35	74	63
1.14	Req'd. Rate of Return	"	Qn.32a/34	74	57
1.15	Ann. Exports by Sector & Lifeform: 89-93	"	Qn.32a/33b	74	29/35/40/49/68[a]
1.16	Ann. Bal. of Trade by Sector & Lifeform: 89-93	"	Qn.32a/33b-c	74	29/35/40/49/68[a]
1.17	Ann. Prod'y. by Sector & Lifeform: 89-93	"	Qn.32a/33b/6b	74	29/35/40/49/68[a]
1.18	Ann. Sales by Lifeform & Sector: 89-93	"	Qn.32a/7e	74	29/35/40/49/68[a]
1.20	Ann. Investment by Sector & Lifeform: 89-93	Firms in current prod'n.	Qn.18/20a-c	64	23/29/32/39/51[a]
1.25	Cost of Lifeforms by Type & Sector	"	Qn.18/20a-c	64	23/29/32/39/51[a]
1.21	Ann. R&D Costs by Lifeform & Sector: 89-93	Firms active in R&D	Qn.7e/11/12a-b	132	69/83/99/112/124[a]

Note:

[a] Sample response varies by year (1989 to 1993 respectively).

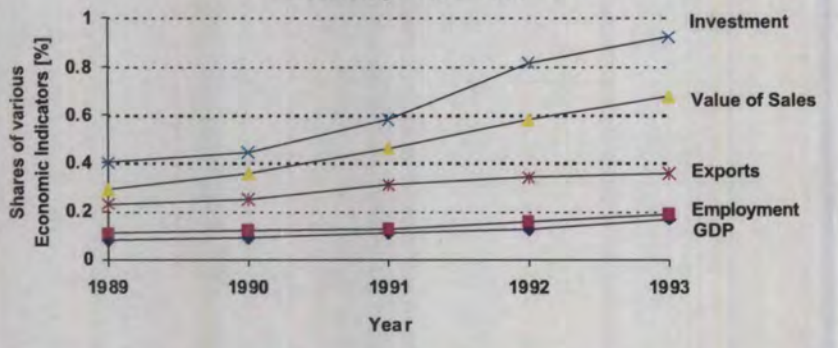
Since the survey was cross-sectional in nature (i.e., at one point in time — February 1994), and respondents were asked to provide historical information (1989 to 1993) on various aspects of their business (e.g., sales, R&D, production costs, exports and imports), the estimation errors will grow the further back in time the respondent is asked to report on. This is evident from the above annual sample responses. In general, when the respondent did not know or did not specify an answer, the response was not included in the analysis. Non-response could mean either that the company was not in business at that time, or that the requested data were not available. In both cases, there would be no effect on the estimate of the mean. In the latter case, since it would be impossible to know whether the response, if provided, would raise or lower the average for the information in question, the procedure should not lead to any systematic bias. Instead, there would be an increase in the standard error of the estimate.

Since this survey only picks up the 1994 cohort, the question arises as to whether or not information is lost about earlier cohorts some of whose members may have gone out of business by 1994. Given the long lead times for biotechnology, this point would tend to be valid only for small firms in start-up mode (i.e.,

1.4.2 Contribution of the Biotechnology Industry to the Canadian Economy

Table 1.3 provides a performance review of the Canadian biotechnology community over the 1989 to 1993 period. Figure 1.2 illustrates that, for five of six economic indicators [gross domestic product (GDP), employment, value of sales, investment and export earnings], the data are a glowing testament to the community's phenomenal growth and its increasing contribution to the overall economic life of the country. Moreover, this economic performance has taken place during the worst recession since World War II. However, this study found a growing trade imbalance in biotechnology which is a significant trade policy issue.

Figure 1.2
Biotechnology Community's Share of the Canadian Economy: 1989-1993



The highlights of the contribution of biotechnology to the Canadian economy include:

- Biotechnology's share of GDP steadily increased from 0.08 percent in 1989 to 0.17 percent in 1993. This represents an average growth rate of over 20 percent per year in the community's contribution to Canada's overall GDP.

- The biotechnology community's contribution to aggregate Canadian employment has grown from 0.11 percent in 1989 to 0.19 percent in 1993, an average growth rate of 14 percent per year.

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exclusively R&D mode). By the time a biotechnology company begins production and sales activity, the likelihood of its demise is very much reduced. Readers are cautioned to bear these qualifying comments in mind when interpreting the results.

Table 1.3

Contributions of the Biotechnology Community to the Canadian Economy: 1989-1993

Canadian Biotechnology Community's Economic Performance	1989	1990	1991	1992	1993
1. Contribution to GDP [($M)	$538	$621	$759	$925	$1,220
1a. Share of GDP (%)	0.08%	0.09%	0.11%	0.13%	0.17%
2. Contribution to Employment	13,785	15,675	16,050	19,900	23,260
2a. Share of Canadian Employment (%)	0.11%	0.12%	0.13%	0.16%	0.19%
3. Value of Sales ($M)	$899	$1,085	$1,298	$1,667	$2,095
3a. Share of Canadian Value of Sales (%)	0.29%	0.36%	0.46%	0.58%	0.68%
4. Investment ($M)	$121	$131	$158	$189	$221
4a. Share of Canadian Investment (%)	0.40%	0.44%	0.58%	0.82%	0.92%
5. Export Earnings ($M)	$373.7	$417.4	$511.1	$625.3	$748.5
5a. Share of Canadian Exports (%)	0.23%	0.25%	0.31%	0.34%	0.36%
6. Balance of Trade ($M)	-$146.5	-$210.4	-$235.2	-$379.2	-$429.7

See Footnote [18] for methodological details.

- During this five-year period, the value of Canadian biotechnology sales grew by an average 24 percent per year.

- During this five-year period, the value of Canadian biotechnology sales grew by an average 24 percent per year.

- The biotechnology community's share of the Canadian value of shipments of manufacture doubled from 0.29 percent in 1989 to 0.68 percent in 1993, representing an average growth rate in share of sales of 24 percent per year.

- The biotechnology community's investment in manufacturing grew by an average 16 percent per year; and its share of Canada's aggregate investment by manufacturing grew from 0.40 percent in 1989 to 0.92 percent in 1993.

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[18] GDP is estimated as the total value of Canadian biotechnology firm sales not including the resale of imported final biotechnology products, minus the cost of inputs, plus the value of supplier export sales. Canadian GDP and employment data were obtained from Department of Finance Economic and Fiscal Reference Tables (August 1993), and Statistics Canada's news release for 1993 economic data. Canadian value of sales data were based on the Canadian value of shipments of manufacture (Statistics Canada Cat. No. 11-210). Canadian investment data were based on total manufacturing investment in Canada (from private and public investment in Canada). Canadian export data were based on exports of goods and services (GDP expenditure based). Canadian balance of trade data were based on the difference between exports and imports of goods and services (GDP expenditure based).

- The biotechnology community's export earnings grew at an average rate of 19 percent per year, and its share of Canada's export earnings increased from 0.23 percent in 1989 to 0.36 percent in 1993, for an average growth rate in biotechnology's export share of 12 percent per year.

- Canada's balance of trade "imbalance" deficit in biotechnology is large and has been growing at an average annual rate of 31 percent.

1.4.3 Ownership and Sectoral Characteristics of the Canadian Biotechnology Community

Table 1.4 shows the ownership structure of the Canadian biotechnology industry in 1993 by size of firm (i.e., number of employees) as estimated from the survey response.

Table 1.4

Type of Ownership and Location of Canadian Biotechnology Firms in 1993

Type of Ownership and Canadian Firm Locations	Size of Firm				
	1-10	11-25	26-100	101+	Total
1. Private	246	47	67	25	385
a] Publicly traded	56	2	31	16	105
b] Privately held[a]	190	45	36	9	280
c] Canadian only	192	35	45	9	281
d] Canadian multinational	26	5	9	6	46
e] Foreign multinational[b]	28	7	13	10	58
2. Public[c]	63	25	36	29	153
3. Canadian locations[d]					
a] Single Canadian location	231	45	69	36	381
b] Multiple Can. locations	78	27	34	18	157
Total	**309**	**72**	**103**	**54**	**538**

Notes:

[a] May include foreign multinationals publicly traded in home countries.

[b] Country of origin with estimated number of firms: United States (24), United Kingdom (4), Switzerland (15), Belgium (3), Sweden (3), France (3).

[c] Includes university-based research groups.

[d] Locations of surveyed companies included Atlantic Canada (Fredericton, Dartmouth, Charlottetown); Quebec (Montreal, Drummondville, Québec City, Sherbrooke, St-Denis-sur-le-Richelieu, Ville-St-Laurent, Rivière Ouelle, Rivière-du-Loup, Laval); Ontario (Toronto, Brampton, Chatham, London, Ottawa, Blenheim); Western Canada (Winnipeg, Saskatoon, Edmonton, Vancouver, Port Coquitlam, Kamloops, Langley).

- There was a total of 385 privately held firms (72 percent) and 153 (28 percent) publicly owned firms (including university-based and government research institutes and companies).

- Of the private firms, 105 (27 percent) were publicly traded, and the other 280 (73 percent) were closely held private companies. Some of these latter firms are foreign multinationals whose shares are publicly traded in their home countries.

- Canadian-owned private firms accounted for 327 of the private firms (85 percent) and, of these, 281 (86 percent) are based exclusively in Canada while the remaining 46 (14 percent) are Canadian-based multinationals.

- A total of 48 foreign multinationals (15 percent) were operating as Canadian biotechnology firms in 1993. About 29 percent had multiple Canadian business locations.

- The distribution of biotechnology firms by size in the universe was: very small (57 percent), small (13 percent), intermediate (19 percent) and large (10 percent).

- Among private firms, the distribution was toward the smaller-sized firm: very small (64 percent), small (12 percent), intermediate (17 percent) and large (6 percent).

- Public firm sizes were also distributed toward the smaller end, but less so than for private firms: very small (41 percent), small (16 percent), intermediate (24 percent) and large (19 percent).

- When examined according to the number of locations, the distribution by size of biotechnology firms for single location firms was very small (61 percent), small (12 percent), intermediate (18 percent) and large (9 percent). For multiple location firms, the distribution was 50 percent, 17 percent, 22 percent and 11 percent respectively. The figures suggest that there are a considerable number of small and intermediate-sized firms with multiple locations operating small additional offices possibly for marketing and distribution purposes.

The survey design permitted the allocation of firm level business into end use markets or economic sectors. Figure 1.3 shows that 48 percent of all Canadian biotechnology firms were in health care, 27 percent in agri-food (i.e., agriculture, aquaculture, and food and beverage), 14 percent in environment and the remaining 11 percent in the resources sector (i.e., energy, forestry, horticulture, mining, and pulp and paper).

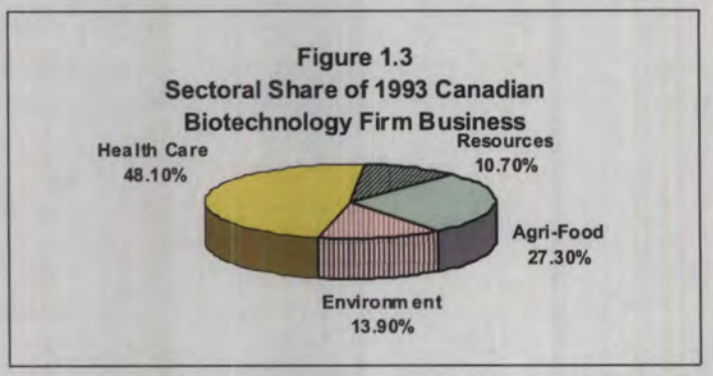

Table 1.5 shows that 73 percent of all firms were in NOM product business, with the remaining 27 percent in GEM business. Most of the 27 percent of GEM firms were concentrated in health care (17.5 percent), followed distantly by agriculture (5.5 percent) and environment (1.6 percent).

Table 1.5

Canadian Biotechnology Firm-Level Business in 1993 Allocated by Sector, Type of Lifeform and Its Patent Characteristics

Sector	Type of Lifeform Product (natural or genetically modified microorganisms or their products) and Patent Characteristics					Total Firm Level Business Allocated by Sector (%)
	Natural Biotech Products (%)	Genetically Modified Biotech Products (%)				
		Innovative	Licensed	Generic	Total	
Agriculture	12.5	3.0	0.9	1.6	5.5	**18.0**
Aquaculture	3.8		0.2		0.2	**4.0**
Energy	0.5	0.1			0.1	**0.6**
Environment	12.3	0.4	0.9	0.3	1.6	**13.9**
Food & beverage	4.6	0.1		0.6	0.7	**5.3**
Forestry	1.4			0.7	0.7	**2.1**
Health care	30.6	10.7	3.2	3.6	17.5	**48.1**
Horticulture	3.1	0.2			0.2	**3.3**
Mining	1.9					**1.9**
Pulp & paper	1.9	0.9			0.9	**2.8**
Totals	**72.6%**	**15.4%**	**5.2%**	**6.8%**	**27.4%**	**100.0%**

Note: See Footnote[19] for methodological details.

[19] Each firm respondent was asked to divide his or her company's business in several ways. First, into 10 end use markets or economic sectors [agriculture, aquaculture (including fisheries), energy, environment, food and beverage, forestry, health care (including diagnostics, therapeutics and vaccines), horticulture, mining, and pulp and paper] into which the company sold its products (or conducted its R&D). Within each economic sector, respondents split their business further into NOM or GEM-based sales or R&D. The GEM business in each sector was subdivided by patent characteristic (innovative, licensed or generic) and by type of organism (animal, plant or microorganism). Last, the total sectoral business was subdivided into microorganisms (or product of microorganisms) having first removed all business in food, drugs, medical devices or pesticide products. This last split enabled economic analyses related to biotech products likely to be affected by the draft CEPA biotech regulations. Each sampled firm had a weight as defined in note 14 which enabled the projection of its responses

Figure 1.4 shows that most of the GEM business was also concentrated in innovative technology (15.4 percent) with generic business taking 6.8 percent and licensed technology the remaining 5.2 percent. Consequently, there were an estimated 147 firms (calculated as 0.274 x 538) engaged in rDNA activity in 1993, and most of this recombinant business (94 firms) was concentrated in health care, with about 30 companies in agriculture and nine in environment. These findings apply to the entire biotech community including firms engaged exclusively in R&D.

Figure 1.4
Share of 1993 Canadian Biotechnology Firm Business by Type of Organism and Patent Characteristic

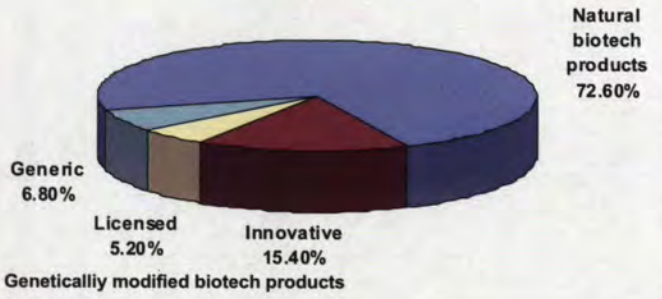

Table 1.6 provides an analysis of the structure of ownership in the Canadian biotechnology industry in 1993 as estimated from our survey. The data are broken down by type of ownership (including public versus private ownership, publicly traded company or not, and owner residency), sector and type of lifeform product business. The table reconfigures information on firm ownership (shown in Table 1.4) and on firm level business (shown in Table 1.5).

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according to any of the above breakdowns.

Table 1.5 shows the distribution of firms in 1993 by sector, type of lifeform and the patent characteristics of the products in the firm's business. The unit of measure in this table is the firm. Consequently, the universe of 538 firms equals 100 percent in the table.

In summary, data are reported by firm classification or by sector. When reported by firm classification, some collapsing of information is necessary due to small numbers. Thus, agri-food is agriculture, aquaculture and food and beverage; and resources is energy, forestry, pulp and paper, and mining. Data for firms falling into the remaining firm classification categories (health care, suppliers, environment and research institutes) are not collapsed. When data are reported by sector, each firm's business is allocated into 10 end-market categories as defined above.

Table 1.6

Number of Canadian Biotechnology Firms in 1993 by Type of Ownership, Sector and Principal Type of Lifeform Business

Sector	Type of Ownership							Total
	Public	Private/ Publicly Traded			Private/ Not Publicly Traded			
		Canadian only	Canadian multinat.	Foreign multinat	Canadian only	Canadian multinat.	Foreign multinat	
PRINCIPAL LIFEFORM BUSINESS: Naturally Occurring Lifeforms								
Agriculture	21	6	2	1	23	4	9	67
Aquaculture					14			20
Energy					2			3
Environment	11	16	3		27	13	2	67
Food & beverage	2	2	3		15		2	25
Forestry	1				5		2	8
Health care	41	29	4	9	55	9	16	165
Horticulture	5	8	1		5			17
Mining	3	6			3			10
Pulp & paper	2			2	4			10
Total	**86**	**67**	**14**	**12**	**152**	**26**	**32**	**391**
PRINCIPAL LIFEFORM BUSINESS: Genetically Modified Lifeforms								
Agriculture	9	7		2	8	1	5	30
Aquaculture					1			1
Energy								
Environment	2				7			9
Food & beverage						4		4
Forestry	4							4
Health care	50	16	1	2	23			94
Horticulture	1							1
Mining								
Pulp & paper	1						5	5
Total	**67**	**23**	**1**	**4**	**39**	**5**	**10**	**147**

Note: Numbers may not add up due to small sample sizes and rounding errors.

Of the estimated 391 firms in the Canadian biotechnology industry in 1993 using natural lifeform products, approximately 86 were publicly owned, 93 were privately owned (and publicly traded) and 210 were privately owned (and not publicly traded). Of the 147 biotechnology firms in the rDNA business, approximately 67 were publicly owned, 28 were privately held (and publicly traded), while 54 were privately held (and not publicly traded). From a competitiveness standpoint, it is important to note that there were the equivalent of 68 private, Canadian-owned biotechnology firms in 1993 engaged in rDNA product business. Of these, six were Canadian-based multinationals (four in food and beverage, and one each in health care and agriculture).

On the natural biotech product side, there were the equivalent of 259 private, Canadian-owned biotechnology firms of which 40 were Canadian-based multinationals (16 in environment, 13 in health care, six in agriculture and three in food and beverage).

1.4.4 Employment Patterns in the Canadian Biotechnology Community

The survey design also permitted the allocation of each company's employment by economic sector, type of biotech product and patent characteristic. This is shown in Table 1.7. When aggregated across companies, total employment in the community in 1993 was estimated to be 23,260 full-time equivalent (FTE) persons.

As indicated in Figure 1.5, almost two thirds of this work force was clustered in the health care sector (65.8 percent) with agriculture and environment accounting for an additional 17.3 percent and 7.3 percent of total employment respectively. Not unexpectedly, most of the work force (69 percent) was allocated by firm respondents into the NOM business with the remaining 7,230 FTEs (31 percent) in the GEM business.

Of the GEM product employment, 4,180 FTEs (57.9 percent) were employed in innovative technology business. Most of the GEM work force was concentrated in the health care sector (80.9 percent) with agriculture (12.1 percent), environment (2.5 percent) and food and beverage (1.5 percent) accounting for most of the remaining GEM employment.

Table 1.7

Total 1993 Employment in the Canadian Biotechnology Community by Sector, Type of Lifeform Product and Its Patent Characteristics

Sector	Type of Lifeform Products (natural or genetically modified microorganisms or their products) and Patent Characteristics					Total Employment Allocated by Sector
	Natural Biotech Products	Genetically Modified Biotech Products				
		Innovative	Licensed	Generic	Total	
Agriculture	3,160	360	180	330	870	4,030
Aquaculture	95		15	10	25	120
Energy	60	10		10	20	80
Environment	1,510	70	50	60	180	1,690
Food & beverage	1,185			105	105	1,290
Forestry	220			15	15	235
Health care	9,450	3,610	1,735	500	5,845	15,295
Horticulture	160				10	170
Mining	90					90
Pulp & paper	100	130	15	15	160	260
Totals	**16,030**	**4,180**	**1,995**	**1,045**	**7,230**	**23,260**

Figure 1.5
1993 Sectoral Employment in Canadian Biotechnology Community by Type of Organism

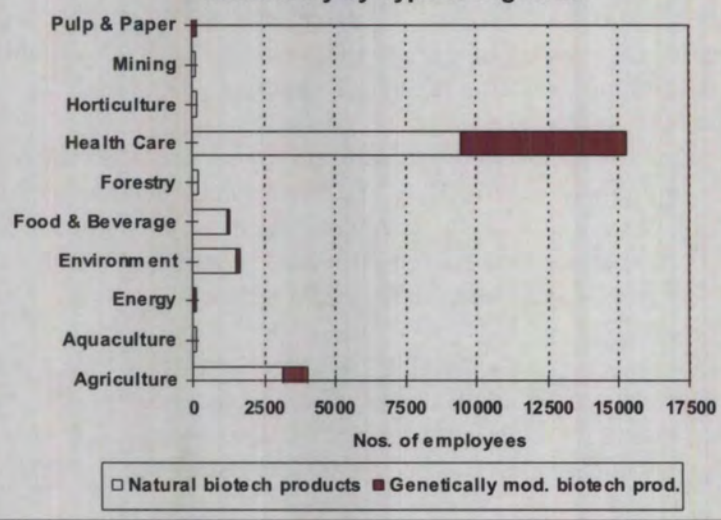

Figure 1.6 highlights the importance of the health care sector to overall employment growth over the 1989 to 1993 period.

Figure 1.6
Annual Employment by Sector in the Canadian Biotechnology Community: 1989-1993

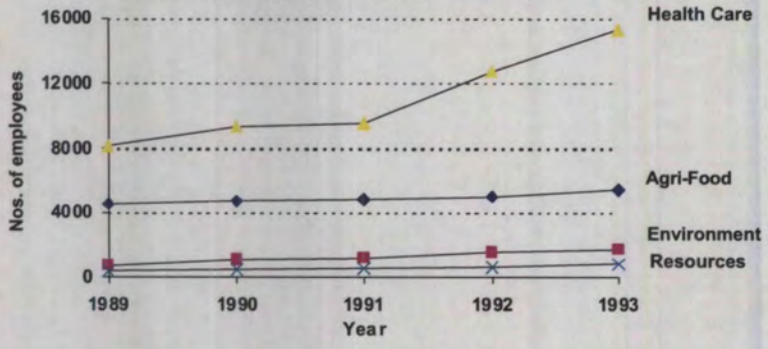

Table 1.8

Total Estimated Annual Employment by Sector in the Canadian Biotechnology Community: 1989-1993

Sector	1989	1990	1991	1992	1993	Average Annual Growth Rate (%) 1989-1993
Agriculture	3,405	3,555	3,585	3,700	4,030	4
Aquaculture	45	60	60	70	120	28
Energy	10	25	30	65	80	68
Environment	700	1,115	1,215	1,510	1,690	25
Food & beverage	1,080	1,090	1,155	1,230	1,290	5
Forestry	30	30	40	60	235	67
Health care	8,200	9,380	9,505	12,720	15,295	17
Horticulture	230	200	250	240	170	-7
Mining	45	70	60	85	90	19
Pulp & paper	40	150	150	220	260	60
Totals	**13,785**	**15,675**	**16,050**	**19,900**	**23,260**	**14**

Respondents were also asked to provide data on the number of full-time and part-time employees in their firms annually since 1989. Table 1.8 shows that FTE employment in the industry has grown from 13,785 in 1989 to 23,260 in 1993 for an average annual growth rate of 14 percent. Health care sector employment grew faster than the overall biotechnology industry's employment, at an annual growth rate of 17 percent, as did environment (at 25 percent), while agricultural and food and beverage employment growth were well below the industry average growth rate (at 4 percent and 5 percent respectively).

1.4.5 Value of Sales Data for the Canadian Biotechnology Community

For each firm reporting sales in 1993, the survey design permitted the allocation of its sales by end use markets, type of biotech product (NOM or GEM) business and the patent characteristics of the GEM business (Figure 1.7 and Table 1.9).

Canadian biotechnology sales totalled $2,095 million in 1993. GEM product sales accounted for $465.1 million, or 22 percent of all sales, and the NOM product business totalled $1,630.1 million or 78 percent of all sales. Nearly all GEM sales were in the health care sector ($408.3 million or 88 percent) with agriculture (at $50.2 million or 11 percent) accounting for most of the remainder. Most NOM sales were also in health care ($902.4 million or 55 percent), although health care's share of the NOM business was less than for the GEM product area. Most remaining NOM business was in agriculture ($539.1 million or 33.1 percent) with food and beverage (at $93.0 million or 5.7 percent) and environment (at $66.3 million or 4.1 percent) well behind.

Figure 1.7
1993 Sales [$M] in Canadian Biotechnology Community by Sector and Type of Organism

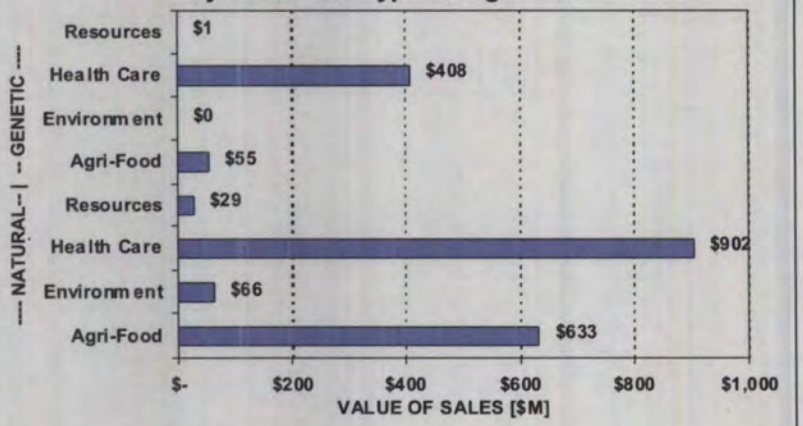

Table 1.9

Total 1993 Canadian Biotechnology Community Sales (in $M) Allocated by Sector, Type of Lifeform and Patent Characteristics

	Type of Lifeform (natural or genetically modified) and Patent Characteristics				
		Genetically Modified			
Sector	**Natural**	**Innovative**	**Licensed**	**Generic**	**Total**
Agriculture	$539.1	$0.8	$17.0	$32.4	$50.2
Aquaculture	0.7	0.1	0.1	0.3	0.5
Energy	4.9	0.1			0.1
Environment	66.3		0.3		0.3
Food & beverage	93.0	0.5	0.1	3.9	4.5
Forestry	6.8				
Health care	902.4	125.1	96.0	187.2	408.3
Horticulture	11.5	0.4			0.4
Mining	4.9				
Pulp & paper	0.5	0.7			0.7
Total	**$1,630.1**	**$127.7**	**$113.5**	**$223.8**	**$465.1**

Table 1.10 shows estimated annual growth in the industry's sales from 1989 levels of $899 million to 1993 levels of $2,095 million. This represents an average annual growth rate of 24 percent. Health care is propelling this rapid increase with an above average growth rate of 27 percent. This sector's share of Canadian biotechnology sales grew from 56.6 percent in 1989 to 62.6 percent by 1993. Agricultural sector sales were below the industry average at 17 percent per annum, as was the food and beverage sector at 8 percent. Conversely, environmental sector sales grew rapidly over this period from $6.4 million (0.7 percent of the 1989 industry) to $66.7 million (3.2 percent of the 1993 industry). Figure 1.8 highlights

the 1989 to 1993 sales growth and shows that the health care sector is the principal driver, with agriculture in second place.

Based on reported sales in 1993, the value of sales averaged $7.2 million for each firm. By company size, very small firms averaged $2.1 million, small firms $0.95 million, intermediate firms $9 million and large firms $25.8 million. Supplier sales in 1993 totalled $652.1 million. The higher sales average for very small firms (as compared with small firms) suggests that the figure is higher due to the presence of distributors. Small, intermediate and large firms are more likely to be engaged in R&D and/or production in addition to sales.

Figure 1.8
Annual Sales by Sector for Canadian Biotechnology Community: 1989-1993

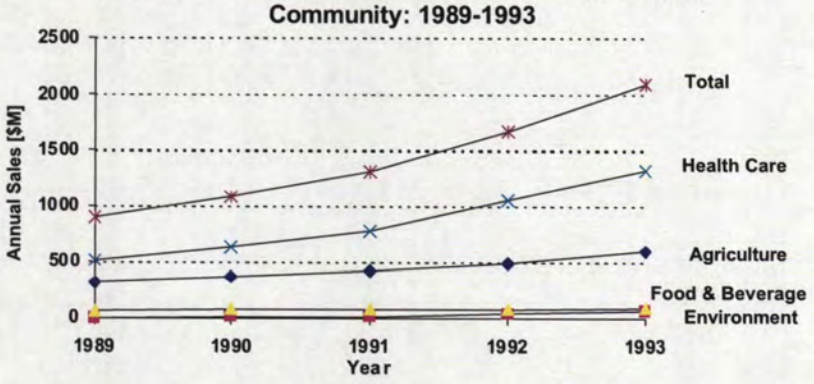

Table 1.10

Total Annual Sales ($M) by Sector for the Canadian Biotechnology Community: 1989-1993

Sector	1989	1990	1991	1992	1993	Avg. Annual Growth Rate: (%): 1989-1993
Agriculture	$311.0	$362.7	$421.3	$482.8	$589.3	17
Aquaculture	0.1	0.1	0.2	0.5	1.2	97
Energy	0.1	0.1	0.2	2.6	5.0	216
Environment	6.4	9.7	13.7	36.6	66.7	80
Food & beverage	72.0	78.9	80.7	82.4	97.5	8
Forestry					6.8	
Health care	508.9	633.5	778.4	1,057.3	1,310.7	27
Horticulture	0.2	0.3	2.5	3.2	11.9	168
Mining				1.2	4.9	
Pulp & paper	0.1	0.2	0.6	0.8	1.2	86
Total	**$898.8**	**$1,085.5**	**$1,297.6**	**$1,667.4**	**$2,095.2**	**24**

Table 1.11 shows the distribution of 1993 industry sales by size of firm across regions of the country. The regional distribution of sales follows population patterns in the country with Ontario and Western Canada showing slightly fewer sales, and Quebec and the Atlantic provinces slightly more. The table also shows that the proportion of sales by size of firm declined in Atlantic Canada as firm size increased. The converse holds true in Quebec. There was no similar pattern for Ontario and Western Canada firm sales.

Table 1.11

Distribution of 1993 Canadian Biotechnology Sales by Region and Size of Firm (%)

	Size of Firm				
Region	**1-10**	**11-25**	**26-100**	**101+**	**Total**
Atlantic	14.0	10.1	8.0	6.0	10.4
Quebec	21.1	29.3	34.4	26.7	27.3
Ontario	36.2	32.7	33.3	35.5	34.6
West	28.6	27.9	24.2	31.8	27.6
Total	**100%**	**100%**	**100%**	**100%**	**100%**

1.4.6 Investment and Profitability in Canadian Biotechnology

Manufacturing firms provided information on their costs of production over the 1989 to 1993 period. The fixed cost component of the costs of production (estimated by each respondent) was used to determine each firm's investment in productive capacity. Table 1.12 shows the estimated 1993 investment in productive capacity for the Canadian biotechnology industry by sector, type of lifeform product and patent characteristic using the firm allocations provided by respondents.

Investment in 1993 totalled $221.4 million and was concentrated mainly in NOM business (93.3 percent). Of the remaining 6.7 percent of investment in biotechnology production estimated to be in GEM business, most was concentrated in innovative technology (52.7 percent), followed by licensed technology (31.1 percent) and generic product technology (16.2 percent). Health care, food and beverage and agriculture sectoral investment accounted for 73.4 percent, 14.8 percent and 9.6 percent respectively of the industry total investment of $221.4 million in 1993.

Table 1.12

1993 Investment in Productive Capacity ($M) for Canadian Biotechnology Community by Sector, Type of Lifeform and Patent Characteristics

	Type of Lifeform and Patent Characteristics				
	Natural	Genetically Modified			
Sector		Innovative	Licensed	Generic	Total
Agriculture	$19.8	$0.1	$1.2	$2.2	$3.4
Aquaculture	0.1				
Energy					
Environment	1.9				
Food & beverage	30.6		0	0.2	0.2
Forestry	0.5		0		
Health care	151.4	7.7	3.3		11.1
Horticulture	0.4				
Mining	0.1				
Pulp & paper	1.7				
Total	$206.5	$7.8	$4.5	$2.4	$14.7

Note: See Footnote[20] for methodological details.

The paltry estimates for investment in manufacturing capacity for innovative recombinant technology products in 1993 underscore comments made during in-depth interviews with industry stakeholders. They reported that development of their firms' recombinant protein health care products was being hindered by their inability to raise the capital necessary to build a manufacturing capability. This frustration has prompted discussions between the health care biotechnology industry in Ontario and the provincial government to build a multi-user fermentation facility for about $70 million using the province's Sector Partnership Fund. If it proceeds, this investment in manufacturing capacity should begin in 1995.

Table 1.13 provides producer firm estimates of annual investment in productive capacity from 1989 to 1993. Total annual investment growth averaged 16 percent over this period, with agriculture and health care investment outpacing the industry's growth at 31 percent and 18 percent respectively. Food and beverage lagged behind at a 5 percent growth rate.

Respondents were asked to consider whether their 1993 level of profitability represented an acceptable return on equity. The results were almost evenly divided with negative responses edging out the positive ones (53 percent stated "yes" and 47 percent said "no"). The negative responses were greatest among health care respondents (the sector showing the greatest employment, sales and investment activity in the Canadian biotechnology industry) and environmental firm respondents (58 percent "no" and 42 percent "yes").

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[20] For firms with production activity, respondents provided annual estimates (1989 to 1993) of their firm's cost of production, and the percentage of these costs in each year allocated to labour and raw material costs. Analysis of the aggregate data revealed that labour and raw material costs were about 50 percent and 30 percent respectively of the cost of production. Investment, defined as the fixed cost of production, was estimated to be 20 percent of the reported cost of production. Since the labour cost fraction of the total costs of production was inversely proportional to the size of firm, the 20-percent estimate of fixed cost's share of total production costs should be interpreted as a global average which most nearly approximates the actual estimate for intermediate-sized firms.

Suppliers had a slightly lower level of negative responses (57 percent to 43 percent) as did resource companies (54 percent to 46 percent). The response was quite positive among agricultural firm respondents (71 percent said "yes"and 29 percent said "no").

The contrast between the agriculture sector respondents and the remaining sectoral players is striking and, coupled with this sector's other economic indicators (growing productivity based on average annual sales growth rates over the 1989 to 1993 period of 17 percent coupled with a corresponding employment growth rate of 4 percent), suggests a stability not present in the rest of the biotechnology industry.

Table 1.13

Annual Investment in Productive Capacity ($M) by the Canadian Biotechnology Community by Sector: 1989-1993

Sector	1989	1990	1991	1992	1993
Agriculture	$7.8	$8.4	$11.9	$16.4	$23.2
Aquaculture					0.1
Energy					0.1
Environment	1.6	1.9	2.1	3.0	2.0
Food & beverage	24.9	23.5	26.7	27.3	30.8
Forestry					0.5
Health care	84.7	95.7	115.5	140.0	162.6
Horticulture	0.3	0.1	0.5	0.7	0.4
Mining					0.1
Pulp & paper	1.6	1.5	1.6	1.6	1.7
Total	**$120.9**	**$130.1**	**$158.3**	**$189.0**	**$221.5**

The survey went on to ask respondents what percentage rate of return on equity their firms looked for, or needed, to remain viable in the market. Table 1.14 breaks down the responses by sector and size of firm. By sector, environmental firms reported the largest requirement (31.2 percent), followed by health care and pulp and paper (27.4 percent), horticulture (26.5 percent), energy (24.9 percent), agriculture (20.7 percent), forestry (19.3 percent), food and beverage (18.4 percent) and mining (15.4 percent). For agriculture and health care sector respondents, the required rate of return on equity decreased with growth in the size of the firm. This suggests that firm size is an indicator of performance and viability for shareholders and the investment community. The small response numbers by other sectoral respondents precluded making any trend statements about those sectors.

Table 1.14

Required Rate of Return on Equity for Canadian Biotechnology Firms in 1993 by Sector and Size of Firm (%)

	Number of Employees per Firm (%)				
Sector	1-10	11-25	26-100	101+	Total
Agriculture	24.2	19.3	21.3	11.7	20.7
Aquaculture	20.0		20.0		20.0
Energy		19.0	28.5		24.9
Environment	30.0	22.0	35.5		31.2
Food & beverage	20.0	16.0	19.0	15.0	18.4
Forestry		18.0	20.0		19.3
Health care	39.0	22.0	24.3	12.4	27.4
Horticulture	25.0	20.0	29.8		26.5
Mining		5.0	18.5		15.4
Pulp & paper		23.5	29.8		27.4

The size of these reported rate of return requirements may come as a surprise to those unfamiliar with the exigencies of the biotechnology industry. Risk of failure is an ever-present and dominant fact of life. Quantifying this risk is a difficult but essential exercise for potential investors. Representatives of the Canadian venture capital community have stated that it is not unreasonable to require at least a 100 percent return on equity on biotechnology firm investments, given the expectation that four out of five such investments will ultimately yield returns ranging from nothing to, at best, treasury bill yields. One published estimate suggests that the failure rate for start-up biotechnology companies exceeds 90 percent. This rate falls to 65 percent after the first year of successful operation (or survival), then to 40 percent after two or three years, and to 20 percent after five or six years.[21]

An investment strategy designed to provide an expected yield of 20 percent return on equity, therefore, has to begin by establishing these higher level requirements. The difference between our survey's reported rate requirements and more "reasonable" investor expectations, as reflected by the performance of other industries, is the market's perception of the added risk of failure for biotechnology firms. To a very real extent, required rates of return in the biotechnology industry are driven upward by this hidden factor which never appears on a firm's statement of operations or its balance sheet. Required rates of return are also driven upward by exogenous factors, such as public debt or interest rates — even further beyond the control of biotechnology companies.

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[21] Ostrach, M. "Financing biotechnology companies." Chapter 3 in *Biotechnology: the science and the business*. Edited by V. Moses and R.E. Cape. Chur, Switzerland: Harwood Academic Publishers, 1991.

1.4.7 Export and Balance of Trade Characteristics of the Canadian Biotechnology Community

Respondents estimated their firms' exports as a percentage of their total sales. Using each firm's allocation of its business across economic sectors and lifeform products, it was possible to produce annual estimates of exported biotechnology goods and services for the years 1989 to 1993 by sector and type of lifeform.

Table 1.15 shows that natural lifeform export sales of goods and services grew by an average annual rate of 19 percent during this period to an estimated $640 million in 1993; corresponding figures for genetically modified lifeform goods and services were 21 percent and $109 million respectively.

The agriculture sector had 58 percent of the 1993 export sales in natural lifeform products ($372 million), health care had 37 percent ($237 million) and environment 3 percent ($20 million). For genetically modified lifeform products, health care had 58 percent of 1993 export sales ($63 million) and agriculture nearly all the remainder at 40 percent ($43 million).

Export sales in biotechnology products originated primarily from Canadian-owned companies (including Canadian multinationals) and from a small number of U.S. and European multinationals. The exports of health care producer respondents included tissue culture media, phospholipids and analytical services, monoclonal antibodies, fermentation bacteria, mutagenic substrates, protein inhibitors, carbohydrates, receptor clones for testing purposes, osteoarthritic and other therapeutics, vaccines, digestive products, inorganic bone material and fractionating equipment.

Table 1.15

Canadian Biotechnology Industry Exports ($M) by Sector and Type of Lifeform: 1989-1993

	Naturally occurring lifeforms					Genetically modified lifeforms				
Sector	**1989**	**1990**	**1991**	**1992**	**1993**	**1989**	**1990**	**1991**	**1992**	**1993**
Agriculture	$265.5	$287.5	$315.4	$337.6	$372.1	$43.0	$46.5	$48.5	$48.8	$43.1
Aquaculture					0.3					0.1
Energy			0.01	1.2	2.5				0.1	0.1
Environment		0.1	0.1	9.9	19.9				0.2	0.3
Food & beverage	3.0	3.5	4.0	4.2	4.1				2.4	2.0
Forestry					0.4					
Health care	54.7	68.7	116.5	174.6	236.8	7.2	11.0	26.4	45.5	63.3
Horticulture	0.2	0.2	0.2	0.1	0.1					
Mining				0.6	3.5					
Pulp & paper										
Total	**$323.5**	**$359.9**	**$436.3**	**$528.2**	**$639.7**	**$50.2**	**$57.5**	**$74.9**	**$97.0**	**$108.9**

Supplier firms also exported health care products including immunological reagents, measurement kits for chemical residues, microbiological media food, immunological products for transplantation, culture media, ELISA, in-vitro diagnostics, products of animal serum, growth components for media and tissue, cancer diagnostics and therapeutics, vaccines, antibodies for diagnostic kits, kits for auto-immune testing, immunological research products, cell separation systems, environmental water pollution tests, antibodies, tissue culture media, enzymes and hematology diagnostics.

Additional exports originated from agricultural firms (e.g., poultry products, bovine semen, embryo research products and insect products), food and beverage (e.g., lactose-free dairy products), mining (e.g., reconstructed ecosystems), environment (e.g., detection equipment for toxic pollutants and soil bioremediation services) and research institutes (e.g., molecular genetic and transgenic animal research, monoclonal antibodies, tissue culture conifers and environmental assessment services).

Table 1.16 shows the balance of trade (exports minus imports) for the industry from 1989 to 1993 by sector and type of lifeform product. There is a significant and growing deficit in health care biotech, both naturally occurring and genetically modified lifeforms, and a stable surplus in agricultural biotech. For natural lifeform products, the balance of trade remained near -$170 million during this period (except for 1992 when it jumped to -$304 million). For genetically modified lifeform products, the balance of trade has moved downward from $18 million in 1989 to -$255 million by 1993.

Table 1.16
Balance of Trade ($M) for the Canadian Biotechnology Community by Sector and Type of Lifeform: 1989-1993

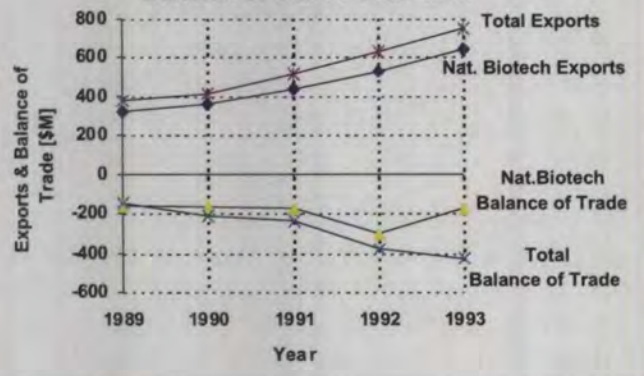
	Naturally Occurring Lifeforms					Genetically Modified Lifeforms				
Sector	**1989**	**1990**	**1991**	**1992**	**1993**	**1989**	**1990**	**1991**	**1992**	**1993**
Agriculture	$263.3	$284.4	$309.9	$330.8	$354.9	$42.9	$46.2	$46.8	$46.7	$41.1
Aquaculture					0.2	-0.1	-0.1	-0.3	-0.5	-0.4
Energy				1.2	2.5					
Environment	-3.2	-3.4	-3.9	5	14.6				0.1	0.2
Food & beverage	-12.3	-8.3	-8.9	-9.2	-13.4	-0.1	-0.6	-0.7	-1.0	-0.9
Forestry										
Health care	-411.5	-436.8	-470.7	-628.0	-532.9	-24.6	-88.0	-102.9	-119.6	-294.5
Horticulture	0.2	0.2	-0.2	-0.1	0.1					
Mining				0.6	0.6					
Pulp & paper	-4.1	-3.8	-4.1	-4.1	-3.9	-0.1	-0.2	-0.3	-0.5	-0.7
Total	**-$164.5**	**-$167.8**	**-$177.7**	**-$303.5**	**-$174.5**	**$18**	**-$42.6**	**-$57.5**	**-$75.7**	**-$255.2**

Note: See Footnote[22] for methodological details.

[22] Respondents provided the value of their firm's sales for the years 1989 to 1993. They also provided estimates of the percentage of these annual sales representing imports and exports. Annual export figures were obtained from the responses on each firm's value of sales. Each producer firm also provided an estimate of the percentage of its total raw material and equipment costs in 1993 which were based on imported goods. Annual import figures were based on the sum of the value of sales based on imports and the costs of production based on imported materials (using the 1993 estimate of imported raw material and equipment costs as a percentage of total raw material and equipment costs applied to the costs of production for all five years). The balance of trade is total exports less total imports.

Figure 1.9 shows a relatively smooth and growing imbalance in trade unaffected by the negative jump in 1992 for natural products. The imbalance for recombinant lifeform products is driving the overall trend to negative growth at an estimated average annual rate of 31 percent. Of course, exogenous factors, such as the slide in Canada's exchange rate, also play key roles in the size of the trade imbalance.

Figure 1.9
Canadian Biotechnology Exports and Balance of Trade: 1989-1993



The 1993 Patented Medicine Prices Review Board (PMPRB) Annual Report noted that Canada's imports of pharmaceutical-related products were worth more than three times as much as its pharmaceutical exports. In 1993, the Canadian pharmaceutical industry exported 11.3 percent ($489.2 million) of its shipments. Imports accounted for 36.9 percent ($1,602.1 million) of the total Canadian market for pharmaceuticals. Our survey shows that a growing portion of this trade imbalance can be attributed to biopharmaceuticals.

The respondent data base was examined for patterns and trends among importers of intermediate and final biotechnology products. Final product imports were clustered among health care respondents and spanned a broad range of product categories including antibiotics, immunological research products, hepatitis B vaccine, therapeutics (e.g., CNS and oncology) and diagnostic imaging. The largest group of these health care importers were foreign multinationals, but some Canadian companies were also included. Supplier firms were also large importers of intermediate products for the health care sector, and included immunological agents (and related products), diagnostic and other testing kits (e.g., for chemical residues, ELISA, immunology and pregnancy), media cultures, chemicals, biochemicals, cell biology products and various equipment categories.

Supplier respondents included both exclusively Canadian firms as well as Canadian and foreign multinationals. To a smaller extent, environmental firm respondents were also importers of enzymes (for pulp and paper applications), other bacterial cultures and enzymes, microbes (for agricultural applications) and environmental equipment. These firms included foreign multinationals and small Canadian companies.

- The percentage of sales based on imports increased with the volume of sales for importers of health care intermediate products (suppliers) and final products, i.e., large importers were also large sellers.

To summarize, the growing dependence of the Canadian biotechnology sector on imports is concentrated in the health care sector and is undoubtedly related to the growing number of high-value biopharmaceutical intermediate and final products emerging from maturing biotechnology industries in the United States and Europe.

1.4.8 Productivity in the Canadian Biotechnology Community

Table 1.17 shows the estimated productivity of the Canadian biotechnology industry defined as the value of sales per employee. The table provides estimates for broad groupings of economic sectors by year and by type of lifeform product. The agri-food sector includes agriculture, food and beverage, and horticulture. The resources sector includes aquaculture, energy, forestry, mining, and pulp and paper.

Table 1.17

Productivity (in $K of sales/employee) in the Canadian Biotechnology Industry by Sector and Type of Lifeform: 1989-1993

	Naturally Occurring Lifeforms					Genetically Modified Lifeforms				
Sector	**1989**	**1990**	**1991**	**1992**	**1993**	**1989**	**1990**	**1991**	**1992**	**1993**
Agri-food	$147	$155	$179	$182	$187	$126	$130	$132	$135	$107
Environment	37	17	21	50	72					
Health care	153	139	170	145	112	16	48	70	74	126
Resources	0.5	4.8	4.8	43	72	12	18	31	42	34
Total	**$147**	**$136**	**$160**	**$148**	**$127**	**$35**	**$60**	**$80**	**$82**	**$122**

Note: See Footnote[23] for methodological details.

For the natural lifeform product business, the data show productivity improvements from 1989 to 1991 followed by successive declines in 1992 and 1993. These declines are driven by health care and suggest a possible rationalization in the near term. The declines in health care are mitigated somewhat by upward productivity trends in agri-food, environment and resources. The data also suggest a growing productivity improvement in the recombinant lifeform product business during the same period. This latter trend appears to be concentrated in the health care sector.

[23] Productivity was defined as sales per firm divided by employment per firm. Per firm sales and employment figures were obtained by finding averages across those firms reporting sales for the year in question. Averages were calculated by broad sectoral grouping, year (1989 to 1993) and type of lifeform (natural versus genetically modified).

1.4.9 Economic Data for Canadian Biotechnology Sectors Marketing Genetically Modified Biotech Products Derived from Animals, Plants or Microorganisms or Their Products

The next five tables (tables 1.18, 1.19, 1.20, 1.21 and 1.22) break down much of the foregoing information for genetically modified products by the type of originating lifeform or its products: animal, plant or microorganism.

Table 1.18

Total Sales of Genetically Modified Lifeform Products for Canadian Biotechnology Firms (in $M) by Type of Originating Lifeform (animal, plant or microorganism) and Sector: 1989-1993

Sector	1989	1990	1991	1992	1993
ORIGINATING LIFEFORM: Animal (or its products)					
Agriculture	$53.1	$58.9	$62.6	$63.8	$58.0
Aquaculture	0.1	0.1	0.2	0.3	0.3
Energy					
Environment					
Food & beverage	0.1	0.2	0.3	6.0	5.1
Forestry					
Health care	21.3	28.0	39.0	45.9	163.2
Horticulture					0.1
Mining					
Pulp & paper					
Total	**$74.6**	**$87.2**	**$102.1**	**$116.0**	**$226.7**
ORIGINATING LIFEFORM: Plant (or its products)					
Agriculture		$0.1	$0.4	$0.3	$0.8
Aquaculture			0.1	0.1	0.1
Energy			0.1	0.1	0.1
Environment					
Food & beverage			0.1	0.1	0.1
Forestry					
Health care	$0.2	0.4	1.0	1.4	1.7
Horticulture					0.4
Mining					
Pulp & paper					
Total	**$0.2**	**$0.5**	**$1.7**	**$2.0**	**$3.2**
ORIGINATING LIFEFORM: Microorganism (or its products)					
Agriculture			$0.7	$0.5	$0.7
Aquaculture			0.1	0.1	0.2
Energy		0.1	0.1	0.1	0.1
Environment				0.3	0.4
Food & beverage			0.1	0.1	0.1
Forestry					
Health care	$9.9	15.2	44.0	85.8	233.0
Horticulture					
Mining					
Pulp & paper	0.1	0.2	0.4	0.6	0.8
Total	**$10.0**	**$15.5**	**$45.4**	**$87.5**	**$235.3**

Table 1.18 provides data on annual total sales for rDNA product firms from 1989 to 1993 by sector and type of originating lifeform. Animal-derived product sales were clustered in health care (for which sectoral sales jumped unpredictably in 1993), agriculture and, to a small extent, in food and beverage. The only other significant cluster of sales was in microorganism-derived products in the health care sector. Sales for plant-derived products were negligible by comparison.

Table 1.19 uses the survey's locative methodology to distribute rDNA firm employment by type of originating lifeform, year (1989 to 1993) and broad sectoral grouping. Not surprisingly, health care had most of the employment (for animal and microorganism-derived products) with agri-food picking up most of the remainder. As before, employment in plant-derived product areas was negligible by comparison with the other product categories.

Table 1.19

Total Employment in Canadian Biotechnology Firms by Type of Genetically Modified Biotech Product (animal, plant, or microorganism) and Sector: 1989-993

ORIGINATING LIFEFORM: Animal (or its products)					
Sector	**1989**	**1990**	**1991**	**1992**	**1993**
Agri-food	490	490	490	490	490
Environment					
Health care	2,475	2,580	2,580	2,700	2,820
Resources					
Total	**2,965**	**3,070**	**3,070**	**3,190**	**3,310**
ORIGINATING LIFEFORM: Plant (or its products)					
Agri-food	45	45	50	60	85
Environment					
Health care	40	45	50	60	85
Resources		75	85	90	125
Total	**85**	**165**	**185**	**210**	**295**
ORIGINATING LIFEFORM: Microorganism (or its products)					
Agri-food	345	345	330	370	370
Environment	115	90	105	170	180
Health care	1,170	1,650	1,815	2,475	2,940
Resources				90	90
Total	**1,630**	**2,085**	**2,250**	**3,105**	**3,580**

Table 1.20 shows total investment by type of originating lifeform, year and broad sectoral grouping. Investment is clustered in the health care sector (for animal and microorganism-derived products) and in agriculture (for animal-derived products only). Again, the plant-derived product area shows little investment activity.

Table 1.20

Total Investment for Canadian Biotechnology Firms (in $M) by Type of Genetically Modified Biotech Product (animal, plant, or microorganism) and Sector: 1989-1993

Sector	1989	1990	1991	1992	1993
ORIGINATING LIFEFORM: Animal (or its products)					
Agri-food	$2.6	$2.9	$3.4	$3.5	$3.5
Environment					
Health care	5.4	6.1	7.0	7.7	7.7
Resources					
Total	**8.0**	**9.0**	**10.4**	**11.2**	**11.3**
ORIGINATING LIFEFORM: Plant (or its products)					
Agri-food	$0.2	$0.1	$0.1	$0.1	$0.1
Environment					
Health care				0.1	0.3
Resources					
Total	**$0.2**	**$0.1**	**$0.1**	**$0.2**	**$0.4**
ORIGINATING LIFEFORM: Microorganism (or its products)					
Agri-food				$0.1	$0.1
Environment					
Health care	$1.8	$2.1	$2.4	2.5	3.1
Resources					
Total	**$1.8**	**$2.1**	**$2.4**	**$2.6**	**$3.2**

Table 1.21 shows total R&D costs (for rDNA biotech product firms reporting R&D activity) by type of originating lifeform, year (1989 to 1993) and sector. Most R&D expenditures were clustered in the health care sector (in the animal and microorganism-derived product categories). The agriculture sector is well behind with R&D activity in all three categories. Still further behind is the environment sector with some R&D effort in the area of microorganisms.

R&D expenditures were substantial in relation to sales for rDNA product companies. In 1993 for instance, animal product R&D costs ($131.8 million) were 58 percent of sales for rDNA firms in this category. Similarly, microorganism product R&D costs ($177.3 million) were 75 percent of sales for corresponding firms. And plant product R&D costs ($23 million) were over seven times greater than sales ($3.2 million) for rDNA firms engaged in plant genetics. This investment in discovery research and its development bodes well for Canadian biotechnology.

Table 1.21

Total R&D Costs for Canadian Biotechnology Firms (in $M) by Type of Genetically Modified Product (animal, plant or microorganism) and Sector: 1989-1993

Sector	1989	1990	1991	1992	1993
ORIGINATING LIFEFORM: Animal (or its products)					
Agriculture	$12.5	$12.1	$19.4	$15.5	$15.5
Aquaculture					
Energy					
Environment	1.0	1.0	1.0	0.9	0.9
Food & beverage				0.2	0.2
Forestry					
Health care	99.7	105.6	101.0	107.1	115.4
Horticulture					
Mining					
Pulp & paper					
Total	**$113.2**	**$118.7**	**$121.4**	**$123.7**	**$131.8**
ORIGINATING LIFEFORM: Plant (or its products)					
Agriculture	$1.3	$5.1	$5.0	$10.5	$12.9
Aquaculture					
Energy			0.1	0.1	0.2
Environment	0.4	1.3	3.1	2.4	2.4
Food & beverage					
Forestry	0.5	0.7	0.7	0.8	1.0
Health care	1.1	1.1	1.0	2.2	3.3
Horticulture	0.1	0.1	0.1	0.1	0.1
Mining					
Pulp & paper		3.1	3.5	2.9	3.1
Total	**$3.4**	**$11.4**	**$13.5**	**$19.0**	**$23.0**
ORIGINATING LIFEFORM: Microorganisms [or their products]					
Agriculture	$24.8	$27.7	$29.0	$29.0	$29.1
Aquaculture	0.1	0.1	0.1	0.1	
Energy		0.1	0.1	0.2	0.3
Environment	9.3	9.3	8.7	9.7	9.5
Food & beverage					
Forestry					
Health care	64.8	78.1	80.2	88.5	137.7
Horticulture					
Mining					
Pulp & paper	0.2	0.3	0.4	0.7	0.7
Total	**$99.2**	**$115.6**	**$118.5**	**$128.2**	**$177.3**

1.4.10 Economic Data for Biotechnology Firms Subject to CEPA Regulations

Tables 1.22 and 1.23 provide additional information on Canadian biotechnology firms in 1993 which were producing (or conducting research on) biotechnology products not including food, drugs, medical devices and pesticides. These products are subject to CEPA regulations and are of interest. The exclusions effectively eliminate all activity in the agri-food and health care sectors. For the remaining firms in the environment and resource

sectors, Table 1.22 provides information for 1993 on the cost of lifeforms, total exports, balance of trade, productivity and type of ownership. For these sectors, 1993 exports were $26.6 million and were only partially offset by imports since the overall balance of trade was $13.4 million.

Table 1.22

1993 Economic Indicators for Canadian Biotechnology Firms Using Microorganisms or Their Products (excluding firms producing foods, drugs, medical devices and pesticides)

Economic Indicator	Value in 1993
1. Cost of lifeforms ($M)	$0.7M - $1.0M
2. Total exports ($M)	$26.6M
3. Total imports ($M)	$13.2M
3. Balance of trade ($M) (exports-imports)	$13.4M
4. Productivity (1993 Sales/full-time equivalent employee)	$65K/empl.
5. Ownership	**No. of Firms**
Publicly owned	30
Privately owned/publicly traded/Canadian only	30
" / " /Canadian multinational	4
" / " /foreign multinational	2
" /privately held /Canadian only	53
" / " / Canadian multinational	13
" / " / foreign multinational	9

Productivity at $65K/employee is not as high as in the agri-food and health care sectors, but has been increasing (see Table 1.16) and should continue to increase given improving knowledge in bioremediation technologies. An estimated 111 of the 141 biotechnology firms in this broad resource grouping are privately owned. Of these, 100 are Canadian.

Table 1.23 provides further economic data by each sector in 1993 by number of firms, sales, number of employees, investment and required rate of return on equity. Investment activity is still slight for both the environment and resource sector firms suggesting that the industry is still in its infancy. In the environment sector, the high requirement on rate of return (at 31.2 percent) is probably deterring investment.

Table 1.23

Additional 1993 Sectoral Economic Indicators for Canadian Biotechnology Firms Producing Microorganisms or Their Products (excluding foods, drugs, medical devices and pesticides)

Sector	No. of Firms	Sales ($M)	No. of Employees	Investment ($M)	Required Rate of Return on Equity
Environment	81	66.7	1,690	2.0	9.4
Resources	60	29.8	735	2.8	21.8

1.5 Suppliers of Inputs to Biotechnology Industry

In 1993, the supplier portion of the biotechnology community was estimated to have $652 million in sales, and employed 6,400 FTE persons.

A sub-sample of firm respondents was contacted by telephone following the survey to obtain information on the cost of lifeforms in their companies' overall costs of production (for producers of final biotechnology products, and for suppliers involved in the production of intermediate biotechnology products). For research institutes, respondents were asked to provide estimates of the cost of lifeforms in their overall R&D costs. Because of the small sample size and the variability in responses, findings are reported in Table 1.24 in the form of ranges encompassing low and high respondent estimates. Lifeform costs are clustered in the natural lifeform category and, within broad reporting sectors, in the agri-food, research, supplier and health care sectors.

Table 1.24

Range of Estimated Costs of Lifeforms in 1993 by Sector ($M)

Sector	Natural	Genetically Modified
Agri-food	$12.7 - 63.5	$0.9 - 4.5
Environment	0.3 - 0.5	
Health care	3.4 - 10.2	0.3 - 0.8
Resources	0.4 - 0.5	
Research	7.9 - 23.8	3.3 - 10.0
Suppliers	2.9 - 14.7	0.2 - 1.1

Note: See Footnote[24] for methodological details.

[24] The cost of lifeforms was estimated as a fraction of the cost of production for producer and supplier companies, and as a fraction of R&D costs for research firms. An additional follow-up telephone survey of selected firm respondents was undertaken to provide informed estimates of the range for the cost of lifeforms as a fraction of each firm's cost of production (or R&D). Firms were selected to include key sectors and different firm sizes. Respondents were unable to distinguish between natural and genetically modified biotech products so the same ranges were used for both. For environmental and resource-based firms, the survey reported in *Biotreatment News* (Devine, Katherine. "Bioremediation market forecast at $2 billion to $3 billion." *Biotreatment News*, October 1993, pp. 4-6) provided a range of estimates from which the fractional costs for lifeforms were obtained. These fractions are shown below.

Cost of Lifeforms as a Percentage of the Cost of Production by Type of Lifeform and Firm Classification

Firm Classification	Type of Lifeform	
	Natural	Genetically Modified
Agri-food	5% - 25	5% - 25
Environment	3.4 - 4.7	
Health care	1 - 3	1 - 3
Resources	3.4 - 4.7	
Research	1 - 3	1 - 3
Suppliers	2 - 10	2 - 10

Table 1.25 shows the ranges of estimated total cost of lifeforms in 1993 for Canadian biotechnology firms across broad sectoral groupings and by type of originating lifeform. Research institutes were estimated to have the greatest costs in all three categories.

Table 1.25

Total Cost of Lifeforms ($M) in 1993 for Canadian Biotechnology Firms by Type of Genetically Modified Product (animal, plant or microorganism) and Sector

	Originating Lifeform		
Sector	**Animal**	**Plant**	**Microorganism**
Agri-food	$0.4 - 1.8	$0.1 - 0.3	$0.5 - 2.4
Environment			
Health care	0.1 - 0.3	0.0 - 0.1	0.2 - 0.4
Resources			
Research	1.3 - 3.9	0.2 - 0.7	1.8 - 5.3
Suppliers	0.1 - 0.4	0.0 - 0.1	0.1 - 0.6

Note: See Footnote [25] for methodological details.

Respondents were asked to rate the dependency level of each of their leading raw material and equipment suppliers on sales to the Canadian biotechnology industry. Dependency levels were ranked on a scale from 1 to 5 with 1 being not dependent at all, 2 slightly dependent, 3 moderately dependent, 4 highly dependent and 5 exclusively dependent.

The overall mean response was 2.2 indicating below moderate dependence of leading raw material and equipment suppliers to the Canadian biotechnology industry. Agriculture sector respondents had a higher dependency level (mean value of 3.0) than did other sectoral respondents, with supplier respondents second (mean value of 2.4). Health care respondents had a slight dependency level (mean value of 1.9) and resource sector respondents were even lower (mean value of 1.7). Supplier dependency levels increased slightly with size of responding firm from small (mean value of 2.1) to intermediate (mean value of 2.4) to large (mean value of 2.6).

To summarize, supplier companies to the Canadian biotechnology industry are slightly to moderately dependent on their sales to this industry. To reduce their dependency and smooth out sales variability, these companies market to a range of industries of which biotechnology is only one.

On the other hand, biotechnology firms have fewer choices for their raw material and equipment needs and, in some instances involving small fledgling companies, see themselves as highly dependent on their suppliers. For instance, a biotechnology company in the agricultural sector involved in micropropagation of plants and plant culture technology viewed itself as highly dependent on its raw material suppliers in certain areas

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[25] The cost of lifeforms was estimated as a percentage of the cost of production using the percentages shown in Note 24. No distinction was possible between rDNA product firms by type of originating lifeform (animal, plant or microorganism).

(e.g., fertile peat moss). If any generalizations concerning dependency can be drawn from the empirical data in this survey, there appears to be more dependency upstream (from biotechnology producer to supplier) rather than downstream (from supplier to producer). That is, biotechnology companies seem to be more dependent on their supplier companies rather than the converse. Some case examples from direct interviews follow.

A major, Ontario-based supplier of equipment and raw materials to the Canadian biotechnology industry is a subsidiary of a U.S. parent. The firm sells intermediate biotechnology products such as cell culture products, media and products for molecular biology (viz., monoclonal antibodies). It sells predominantly to the health care market (e.g., transplant-related products), and also to veterinarian markets (e.g., animal vaccine components), agricultural markets (for use in transgenic plant work) and to waste management companies. Although 80 percent of its sales go to the research area (and only 20 percent to the biotechnology industry itself), a company spokesperson stated that his firm's future growth is highly dependent on this industry's growth since the research market is based on the vagaries of grant support. Nevertheless, the company appears to have, at most, a modest dependency on the biotech industry in this country.

Another major supplier, based in Quebec, has its parent company in Europe and its North American headquarters in the United States. The company sells equipment (e.g., for chromatography and electrophoresis) and molecular biology materials (viz. DNA sequencing) to the Canadian biotechnology industry. The equipment is produced in Sweden and the molecular biology materials in Milwaukee. The firm sells to the health care market (mainly to research centres including government research institutes) and to private industry (about 20 percent of sales). A company spokesperson emphasized his firm's major dependency on the biotechnology industry.

A small Ontario-based, all-Canadian biotechnology supplier sells transplant immunological products mainly to immunological researchers based in hospitals and universities and, to a smaller extent, to researchers in biotechnology companies. Its sales include reagents, monoclonal antibodies, cell separation media, serum and animal blood cells. The company views itself as highly dependent on the biotechnology research community.

An Ontario-based raw material supplier produces high purity solvents in Canada in addition to distributing lab chemicals (e.g., reagents, acids, organic and inorganic chemicals) from the United States, Germany and Switzerland. The company sells to research laboratories in universities and hospitals, pharmaceutical companies and some biotechnology companies. It views itself as moderately dependent on the Canadian biotechnology industry's viability.

Another Canadian raw material and equipment supplier has its head office in Ontario and warehouses in locations across the country. Its product manager for environment and microbiology said that the company's business with the biotechnology industry is about 25 percent (with sales to, for example, the National Research Council and the Alberta Research Council) and a further 25 percent in health care (selling to, for example, Connaught Laboratories). Some of the health care sales are biotechnology related. The company sells

media for fermentation used to produce antibiotics or vaccines. On the environmental side, it sells water testing kits for trace metal testing. The company is only moderately dependent on the biotechnology industry, and views the biotech field as a growth area.

An American subsidiary supplier company based in Ontario manufactures and distributes products to the laboratory industry. Product areas include glass and plasticware, chemicals (e.g., lab reagents and chromatography) constant temperature equipment, media, weighing systems, diagnostic kits (e.g., virology testing kits), systems for titration (filtration and water treatment), general lab consumables and DNA amplification systems. The company's markets include hospital and private laboratories (for diagnostic systems), university and government laboratories (for educational and research purposes), industrial laboratories and the pharmaceutical industry. Less than 10 percent of its products are manufactured in Canada. It views its markets as highly diversified and itself as, at most, slightly dependent on the Canadian biotechnology industry.

A distributor-type supplier, a division of a German parent, is based in Ontario and sells mainly to the pharmaceutical industry. The company sells lactose and other generic products (e.g., gravol, caffeine and ergot) and does not view itself as dependent on the biotechnology industry.

Another biotechnology company supplier reported his firm's dependence on earlier stage suppliers (e.g., university research laboratories and equipment suppliers). Similarly, another supplier reported his company's dependence on fermentator equipment from Germany.

An illuminating discussion was conducted with the owner–operator of a small Canadian-owned supplier company which produces and distributes lab diagnostic kits and consumables to hospitals, laboratories and clinics across the country. He reported a cost squeeze for his firm related to cost containment efforts in his principal market (the Canadian hospital industry). He indicated that labour productivity was another factor affecting his firm's profitability.

1.6 Users of Biotechnology Products

To obtain some sense of the potential impact of granting intellectual property rights (IPRs) on higher lifeforms and of the proposed CEPA regulations on the availability of products to users, we asked survey respondents to provide information on the end use markets into which they sold their intermediate or final biotechnology products.

It was not possible to give the various responses a priority rating. However, health care companies stated that they sold to agriculture; research groups; laboratories including university, government, diagnostic and related health care, private, research (including pharmaceutical research), hospital, health care and public health labs; hospitals (pharmacy and procurement); physicians' offices; industrial consumers and cosmetic markets.

Agricultural biotechnology company respondents indicated the following markets: farmers, aquaculture, cattle breeders, retail, horticulture, greenhouses, forestry, feed industry, brewing and distillery industries.

In general, supplier firms covered nearly all markets into which all sector-specific biotechnology companies sold their own products or technologies. In particular, supplier respondents indicated the following markets: agriculture, laboratories (as above), hospitals, physicians' offices, food and beverage (and processing) industries, farming, home consumers, retail, cattle breeders, industrial consumers, seed processing, textile processing, cosmetics, forensics, veterinarians, pharmaceutical and other biotechnology companies.

Environmental biotechnology firms indicated the following markets: pulp and paper, oil refineries (and manufactured gas facilities), consumers, chemical industry, mining industry, government, municipalities, industrial consumers, home consumers, agriculture and greenhouses.

Survey respondents in the environmental sector noted more frequently than any other sectoral respondents (57 percent) the presence of close non-biotechnology substitute products or technologies for products or technologies they were currently providing. In terms of frequency of positive response to this question, the environmental sector was followed by the health care sector (41 percent) and supplier firms (30 percent). Note that the availability of non-biotechnology substitute products in all sectors may mitigate the effects of granting biotechnology patents. Examples of close non-biotechnology product or technology substitutes and their sectors as provided by respondents include the following.

- **Environmental Sector:** pollution detection via other technologies, bioremediation by alternative technologies (e.g., soil venting), other forms of composting, waste or peat moss, incineration, washing and burying.
- **Forestry Companies:** artificial fertilizers.
- **Health Care Sector:** lab animals, reagents, anti-irritants, sun block and moisturizers, hepatitis B vaccine by blood product vaccine and osteobiological by natural bone.
- **Horticulture:** endomycorhyzae.
- **Mining Sector:** wastewater treatment plant.
- **Research Firms:** seed orchids.
- **Supplier Companies:** protein purification by streptavidin, chlorine (or other biocide), non-biotech kits for lab sampling, ELISA tests by radio-immune assays, new seed varieties, other cell separation systems and resin (polydrene).

CHAPTER 2

INTERNATIONAL COMPETITIVENESS OF THE CANADIAN BIOTECHNOLOGY COMMUNITY

2.1 Introduction

To participate fully in a global economy, a domestic environment conducive to production must meet three conditions. Rugman and D'Cruz[26] identify these conditions as:

- access to leading-edge technologies;
- a well-educated labour force; and
- a fiscal and statutory climate that encourages savings and investments.

They go on to note that globalization of the world economy has been due, in large part, to the expansion of multinational corporations since the end of World War II. These multinationals operate in several countries at the same time and provide a kind of global nervous system to diffuse technologies rapidly. Another major factor in market globalization has been the trade expansion made possible by a series of agreements beginning with Bretton Woods in October 1947 which established the General Agreement on Tariffs and Trade (GATT) among some 23 countries. National tariffs which, at that time averaged 40 percent to 50 percent, were gradually reduced through eight successive multilateral trade negotiations. Trade expansion has also received a major impetus in Canada from unfettered access to the North American continental market, made possible by the Free Trade Agreement (FTA) of 1990 and the North American Free Trade Agreement (NAFTA) of 1993.

Rugman and D'Cruz also look at the effect fiscal and political factors have on Canada's international competitive performance. They highlight the linkages between the federal government's budget deficits, high interest rates and high exchange rates all of which detract from Canada's competitiveness. They also point to opportunities for diversification in Canada's economy to develop regional industrial clusters. Through efficient and innovative small and medium-sized businesses, these clusters can provide value-added intermediate products and quality industrial services to aid the performances of larger transnationals. Unlike the more highly diversified American economy, Canada has developed only one major industrial corridor along the Montreal–Windsor axis. With the development of regional opportunities and productivity, other clusters can emerge in Quebec, the Maritimes and the West.

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[26] Rugman, A.M. and J.R. D'Cruz. *New Visions for Canadian Business: Strategies for Competing in the Global Economy.* Toronto: Kodak Canada Inc., 1990; Rugman, A.M. and J.R. D'Cruz. *Fast Forward: Improving Canada's International Competitiveness.* Toronto: Kodak Canada Inc., 1991; Rugman, A.M. and J.R. D'Cruz. *New Compacts for Canadian Competitiveness.* Toronto: Kodak Canada Inc., 1992.

Rugman and D'Cruz conclude that internal management structures within organizations need to be revitalized in order to improve Canada's international competitiveness. This will require the retraining of workers and managers to develop a broader global mind set to become globally competitive.

Using a construct called the World Competitiveness Scoreboard (WCS), a Swiss-based consortium has developed a yardstick for measuring the international competitiveness of industrialized and newly emerging economies.[27] The WCS measure is constructed from country-specific macro-economic data (about two thirds of the variables) and from the opinions of business executives in each country (about one third of the variables).

Using this measure, Canada's rank among OECD countries slipped from fourth place in 1989, to fifth in 1990 and 1991 (behind Japan, Switzerland, United States and Germany), to 11th in 1992 and 1993, and to 14th place in 1994. When the ranking was expanded to include new competitors from Asia, Latin America and Eastern Europe, Canada was pushed down to 16th place by Hong Kong and Singapore, Asia's two fast-growing city states.[28] In order, the 1994 rankings were: United States, Singapore, Japan, Hong Kong, Germany, Switzerland, Denmark, the Netherlands, New Zealand, Sweden, Norway, Austria, France, Britain, Australia, Canada, Malaysia, Taiwan, Ireland and Finland.

The WCS defines business competitiveness at the firm or enterprise level as "the ability to design, produce and market goods and services, the price and non-price characteristics of which form a more attractive package than those of competitors."[29] This definition highlights the dominant role played by a firm's customers in determining its competitiveness. Where a firm's delivered cost of product is comparable with its competitors, quality will determine consumer preference. As competitors reduce their costs, the firm must improve its product's quality or lower its own costs to preserve its market share.

A firm's ability to develop and enhance its competitiveness is also influenced by the domestic environment in which it operates. Beyond the firm, the country's competitiveness emerges out of interactions between its national institutions (e.g., governments, universities, unions and research institutes) and the policies and strategies of business firms that develop products and services for the marketplace.

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[27] Crane, David. "Canada's losing edge, study says." *The Toronto Star*, September 7, 1994, pp. C1-C2; Little, B. "Canada slips in world rankings." *The Globe and Mail*, September 7, 1994, pp. B1-B16; Rugman, A.M. and J.R. D'Cruz. *New Visions for Canadian Business: Strategies for Competing in the Global Economy.* Toronto: Kodak Canada Inc., 1990; Rugman, A.M. and J.R. D'Cruz. *Fast Forward: Improving Canada's International Competitiveness.* Toronto: Kodak Canada Inc., 1991; Rugman, A.M. and J.R. D'Cruz. *New Compacts for Canadian Competitiveness.* Toronto: Kodak Canada Inc., 1992.

[28] Crane, David. "Canada's losing edge, study says." *The Toronto Star*, September 7, 1994, pp. C1-C2; Little, B. "Canada slips in world rankings." *The Globe and Mail*, September 7, 1994, pp. B1-B16

[29] Crane, David. "Canada's losing edge, study says." *The Toronto Star*, September 7, 1994, pp. C1-C2

The WCS consists of 10 principal factors (derived from 381 criteria) that permit a closer examination of Canada's underlying competitive performance:

- the dynamism of the economy;
- industrial efficiency;
- market orientation;
- financial dynamism;
- human resources;
- impact of the state;
- natural endowments;
- international orientation;
- future orientation; and
- socio-political stability.

By 1994, international comparisons using the WCS revealed a number of reasons for Canada's declining performance (Table 2.1). On the positive side, Canada's greatest strength is in its infrastructure where it ranks second among 44 economies, and in its financial markets and services (eighth place). Its weaknesses lie in its domestic economic strength (15th place), people availability and qualifications (17th), internationalization (19th), management (19th), science, technology and research (19th), government (22nd) and productivity growth from 1985 to 1993 (33rd). Productivity is the single most important measure of a country's ability to raise its standard of living.

Canada's overall weak showing reflects its continuing low ranking in key areas: the quality of its business management, its low investment in science and technology, the education and training of the work force and the weakness of government. Management incentives are heavily geared to short term results. In contrast, incentives in Japan, Malaysia, Singapore, Hong Kong, Switzerland and Sweden encourage long-term results.

Canada ranked 18th in R&D spending, allocating 1.49 percent of its GDP to R&D. Canadian companies were found to be weak in forging links with universities. Likewise, Canadian companies were much less likely than Japanese, Swiss, Swedish or German companies to co-operate in developing new technology. Education and training is also weak in Canada, ranking 17th overall — well behind Singapore, Denmark, Germany and Japan. Canada's ranking on quality of education was low, with a perceived failure of the education system to meet the needs of a competitive economy. Both skilled workers and competent senior managers were said to be difficult to find. Canadian companies, for their part, got poor marks for their efforts at training workers. Canada ranked 31st — well behind the leaders.

This perspective on Canada's overall competitiveness serves as a useful basis for comparison with the views of Canada's biotechnology community. Later sections of this report review those factors which, according to the biotechnology firm respondents to our survey, had an affect on the international competitiveness of their businesses.

Table 2.1

Canada's World Competitiveness in 1994

Where Canada Leads	Where Canada Is Average
• Low inflation • Willingness by companies to delegate to employees • Good stock markets • Financial systems • Natural resources • Quality of life • Cost of electricity, water, telephones • Enrolment in higher education • High level of computers per capita • Honest public sector • High level of per capita GDP	• Availability of venture capital • Cost of capital for business • Personal security • Development of service sector • Illiteracy in population • Quality of employee training • Attention to customer needs by business • Effectiveness of competition policy • Quality of road, rail and air transport • Availability of competent senior managers • Level of investment in modern production techniques • Agriculture and manufacturing productivity levels • Exploitation of information technologies by companies
Where Canada Lags	
• Extent to which educational systems meet needs of the economy • Companies fail to train employees • Adequacy of science education in schools • Lack of innovation reflected in low number of patents for Canadians • Poor workplace motivation • Canadian values do not support competitiveness • Safety in the workplace • Entrepreneurship among corporate executives • Management focus on short-term results • Poor relationship between employers and workers	• Too long to develop new products and bring to market • Corporate credibility low • Taxes too high • Government debt too high • Extremely weak growth in productivity • Government policies slow to adapt to new economic realities • Lack of cross-border strategic alliances by Canadian companies • Inadequate gross domestic savings • Manufacturing base seriously eroded • Weak growth in export of business services

Source: The *World Competitiveness Report 1994* as reported in Crane, David. "Canada's losing edge, study says." *The Toronto Star*. September 7, 1994, pp. C1-C2.

2.2 Situating Canadian Biotechnology Internationally

In this section, we review the international literature to place the Canadian biotechnology sector in a global context. In particular, we have searched for information on (and identified gaps in our knowledge of) the current size of world markets for specific biotechnology products or classes of products, and Canada's share of those markets. We have also attempted to identify the key biotechnology countries, the largest biotechnology firms in those countries and those firms which will or do provide major foreign competition for Canada's domestic biotechnology industry.

The 1990 global market for biotechnology has been estimated at European currency unit (Ecu) 5.1 billion (US$6.5 billion), and was projected to grow to Ecu 83.3 billion (US$105.8 billion) by the year 2000.[30] (Note that US$1 = C$1.4014; Ecu 1 = C$1.8064 as of the close

[30] Kenward, M. "Biotech heads for the big time." *International Management*, Vol. 47, December 1992, pp. 48-51.

March 24, 1995.)

2.2.1 The Biopharmaceutical Industry

It is widely acknowledged that the United States leads the world in the commercialization of biotechnology. It has a strong foundation in the biological and biomedical sciences, a highly competitive pharmaceutical industry that supports biotechnology both in-house and through alliances with new biotechnology firms (NBFs), and has available venture capital to finance biotechnology development.[31] However, despite the fact that many of the first successful biopharmaceuticals originated in the United States, more of these products are now available in Europe than in the United States, particularly monoclonal antibodies (MAbs).[32]

In 1982, the first biotechnology-based drug — recombinant human insulin — was approved for sale in the United States. By late 1991, 15 biotechnology-based drugs and vaccines were on the market. These drugs are all large proteins which, before advances in biotechnology, were either not available at all, not available in large enough quantities or not of sufficient purity for wide use as treatments. The exception, insulin, was available from pig and bovine pancreases.[33] Surveys of the U.S. Pharmaceutical Manufacturers' Association (PMA) indicate that there are over 100 biotechnology drugs and vaccines in human testing for a variety of conditions. Over half of the drugs in development target cancer or cancer-related conditions, and vaccine research is heavily concentrated on finding a vaccine to combat acquired immunodeficiency syndrome (AIDS).

- Table 2.2 shows 1993 biopharmaceutical sales by geographic market. World sales totalled $7.7 billion with the United States commanding the largest share of this market (40 percent). Japan had 28 percent, Europe 26 percent and the remainder of the world (including Canada) had 6 percent.

- Our 1993 survey results showed that the Canadian health care sector had recombinant deoxyribonucleic acid (rDNA) sales of C$408 million (US$300 million) or a 3.9 percent share of the global estimate. This share figure is slightly inflated by the fact that our survey estimates included sales of proprietary technologies and related services. Since Canada is regarded as a "2 percent" pharmaceutical market, this 4 percent share suggests a greater level of acceptance among Canadian formularies for biotechnology products. It also has trade implications related to Canada's proximity to the burgeoning American

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31 Rubin, S. "Biotechnology and the Pharmaceutical Industry." *Cancer Investigation*, 11 (45), 1993, pp. 451-457.

32 Bienz-Tadmor, B. "Biopharmaceuticals go to market: patterns of worldwide development." *Bio/Technology*, Vol. 11, February 1993, pp. 168-172.

33 U.S. Congress, Office of Technology Assessment. *Biotechnology in a Global Economy*. OTA-BA-494, Washington, DC: U.S. Government Printing Office, October 1991.

biotechnology industry.

- Ernst & Young [34] reported some 1,272 U.S. biotechnology companies by the end of 1993 with a total market capitalization of $45 billion (down from a 1992 level of $48 billion). However, only three U.S. firms showed positive net income flow, the largest being Amgen (at $358 million), followed by Biogen ($38 million) and Genentech ($21 million). Although U.S. biotech industry sales totalled $7 billion in 1993, aggregate net income flow was ($3.6 billion).

- Our study reports some 147 Canadian rDNA biotechnology firms in 1993 (including biotechnology supplier firms). Market capitalization for the 32 publicly traded Canadian biotech firms was $2.64 billion (as of December 11, 1993). Total 1993 Canadian recombinant product sales were $408 million.

Table 2.2

1993 Sales of Biopharmaceutical Products by Geographic Region (in US$M)

Product	United States	Europe	Japan	Rest of World[a]	Total
Alpha-interferon	$145	$435	$665	$45	$1,290
Beta-interferon		15	205		220
Erythropoietin	735	305	355	170	1,565
Factor VIII[b]	155	85	25	10	275
Gamma-interferon	5	3	2		10
Granulocyte colony-stimulating factor (G-CSF)	580	125	240	50	995
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	40	20	15	10	85
Hepatitis B vaccine	560	315	135	45	1,055
Human growth hormone	300	340	325	75	1,040
Human insulin	380	280	130	55	825
Interleukin-2	12	20	3		35
Orthoclone OKT3	40	30	5	10	85
Tissue plasminogen activator	165	40	40	20	265
Total	**$3,117**	**$1,993**	**$2,145**	**$490**	**$7,745**

Notes:

[a] Includes Canadian sales.

[b] Includes immunopurified and recombinant versions.

Source: *Spectrum Biotechnology Overview,* Decision Resources Inc., August 16, 1993.

Assuming a "10 percent" market in Canada (based on its population as a fraction of the U.S. population), both sales and market capitalization lag behind the United States. However, there appear to be slightly more biotechnology firms than warranted by population alone (11.6 percent). The comparisons suggest that the Canadian biotechnology industry is lagging in its aggregate development behind the United States. However, the

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[34] Burrill, G.S. and K.B. Lee Jr. *Biotech 94: Long-Term Value, Short-Term Hurdles.* Ernst & Young's 8th Annual Report on the Biotechnology Industry, Ernst and Young, 1993.

disproportionately larger number of Canadian firms suggests a greater share of proprietary technologies capable of development.

The market for many biotechnology-derived drugs is potentially large. Much of this drug development is market-driven (a phenomenon called "market pull"), with a defined and expectant market (e.g., erythropoietin, human growth hormone, insulin, tissue plasminogen activator and recombinant hepatitis B vaccines). Other significantly smaller developments are more technology-driven (or determined by "science push"), with a less defined market opportunity. An example is alpha-interferon which, before biotechnology, could not be isolated in large enough quantities to conduct research to elucidate its biological activities and therapeutic benefits. Thanks to rDNA techniques, it is now mass produced permitting research and clinical trials to progress; rDNA also assists with a better definition of the substance's activity and mechanism of action.[35]

Interleukin-2 (at least 10 interleukins have been identified) is another example of a naturally occurring immune system protein with somewhat uncertain actions but potential effectiveness in the treatment of cancer. Drugs whose market and mechanism of action are not as yet particularly well defined (e.g., interferon, interleukin and tumor necrosis factor) and whose development is technology-driven must be separated from other biotechnology drugs (e.g., erythropoietin, insulin and human growth hormone) whose development is both technology-driven and market-driven.

Another way to describe the difference between products that are market-driven and those that are more technology-driven is in terms of diseases looking for drugs and drugs looking for diseases. With tPA, human growth hormone, human insulin and erythropoietin, the action of the protein was fairly well understood, allowing researchers to focus on one or more specific diseases. In the case of interleukin-2 or tumor necrosis factor, complicated, multiple biological effects have been exhibited, and researchers have had to search for relevant diseases to address.

Until recently, while all approved biopharmaceuticals in the United States were discovered by NBFs, the funding and expertise of larger companies were essential for drug development, and the regulatory and marketing stages. However, since the early 1990s, some U.S. companies have had the resources to field a sales force, which will likely lead to more products being marketed, at least in part, by the companies that developed them. Thus, Amgen's EPO and granulocyte colony stimulating factor (G-CSF), Genentech's tPA, human growth hormone and gamma interferon, Praxis Biologics' (now owned by Lederle, a subsidiary of American Cyanamid) haemophilus influenzae type B vaccine and Immunex's granulocyte macrophage colony stimulating factor (GM-CSF) are, in part, marketed by the biotechnology companies that discovered them. These companies also have agreements with established companies for marketing their products outside the United States and, in some cases, co-marketing in the United States. Eli Lilly, Hoffman-LaRoche, Merck, Ortho Biotech, Schering-Plough, and SmithKline Beecham — all

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[35] Stroh, W.H. "Trends in use of industrial bioprocessing enzymes for the 21st century." *Genetic Engineering News*, September 15, 1994, pp. 10-12.

established pharmaceutical companies — have licensed marketing rights to other approved products from the NBFs that developed them.

The size of the global pharmaceutical market was estimated to be US$150 billion in 1989. The United States is the largest drug market, accounting for about 30 percent of the world market. The European Community (EC) is the second largest total market. Japan is the second largest single-country market, with an approximate 17.6 percent market share. Pharmaceutical products are marketed globally and, in 1989, 34.4 percent of the $51.2 billion in sales by U.S. drug companies were overseas.

The main competitors for the world pharmaceutical market are multinational firms based in the United States, Switzerland (Ciba-Geigy, Sandoz, Hoffman-LaRoche), the United Kingdom (Glaxo) and Germany (Bayer, Hoechst). These huge companies have research, manufacturing and marketing operations worldwide. A focus on penetrating world markets as well as domestic markets is crucial for success in the pharmaceutical industry.[36]

Table 2.3 highlights distinctions between 1993 sales and R&D spending for the major U.S. pharmaceutical and biopharmaceutical companies.

- U.S. biopharmaceutical company sales were 5 percent of the established pharmaceutical company sales.
- Their R&D spending and R&D spending per employee were 28 percent and 680 percent respectively of those of the established companies.
- In contrast to the healthy profits of the pharmaceutical industry, the biopharmaceutical companies mostly experienced losses.
- For these biopharmaceutical firms, R&D spending consumed 67 percent of their sales. In contrast, established firms spent only 11.9 percent of their sales on R&D.

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[36] U.S. Congress, Office of Technology Assessment. *Biotechnology in a Global Economy*. OTA-BA-494, Washington, DC: U.S. Government Printing Office, October 1991.

Table 2.3

Comparison of 1993 Sales, R&D Spending and Profits ($M)
Top U.S. Pharmaceutical and Biopharmaceutical Companies

Companies	Sales ($M)	R&D Spending ($M)	R&D/Employee ($K)	Profit/Loss ($M)
Established U.S. Pharmaceutical Companies				
Abbott Laboratories	8,408	881	17.7	1,399
American Home Products	8,305	663	12.9	1,469
Bristol Myers Squibb	11,413	1,128	22.8	1,959
Glaxo Holdings (6/93)	7,987	1,197	29.9	1,955
Lilly	6,452	955	29.2	491
Marion Merrell Dow	2,818	451	45.9	362
Merck	10,498	1,173	24.9	2,166
Pfizer	7,478	974	24.1	658
Schering Plough	4,341	578	26.7	825
SmithKline Beecham	9,246	863	16.6	980
Syntex (7/93)	2,123	404	39.3	288
Upjohn	3,653	642	34.5	402
Warner-Lambert	5,794	465	13.3	285
Wellcome (8/93)	3,034	484	27.5	621
Total	**91,550**	**10,857**	**25.3**	**13,861**
Top U.S. Biopharmaceutical Company Sellers				
Alza*	220	53	NA	42.9
Amgen	1,374	255	83.3	375
Biogen	136	79	208.7	32.4
Centocor	71	57	113.4	-74.4
Chiron*	240	140	64.3	18.4
Collagen (6/93)	50	9	27.7	9.7
Curative Technologies	31	8	21.0	-4.4
Elan* (3/93)	136	17	22.2	32.3
Enzo Biochem* (7/93)	20	1	6.3	-6.4
Genentech	608	295	117.6	58.9
Genetics Institute* (11/93)	102	100	107.7	-16.9
Gensia Pharmaceuticals	29	54	104.9	-63.3
Genzyme*	270	97	56.5	-6.1
Immunex*	123	419	535.6	-430.3
Int'l Murex Technology*	80	6	10.1	2.7
Life Technologies	206	14	10.7	16.6
Quidel* (3/93)	29	4	16.7	0.4
Scios Nova	48	36	88.1	-36.6
Synergen*	13	88	141.9	-84.2
TSI* (6/93)	58	3	4.4	-32.0
Vertex Pharmaceuticals*	28	23	186.8	2.0
Vestar*	33	17	95.5	-4.6
Total	**4,528**	**3,055**	**173.0**	**-1,583**

Notes:
Results are for the fiscal year ending December 1993, except as noted.
NA means not available.
* means R&D includes customer-sponsored or government-sponsored expenses.

Source: Standard & Poor's Compustat Services (Englewood, CO) as reprinted in *Bio/Technology*, Vol.12, July, 1994, pp.652-655.

The Japanese market has, historically, been difficult to enter without a Japanese partner. As a result, to ensure market presence, U.S. and European companies have collaborated with Japanese companies that dominate their domestic market. For many years, U.S. and European companies increased their presence in Japan by establishing their own marketing forces. In recent years, in a few cases, they built research facilities or acquired a Japanese company. Currently, 24 U.S. pharmaceutical companies operate in Japan and account for about 15 percent of the $33 billion Japanese pharmaceutical market. The domestic Japanese market is still dominated by Japanese companies, and no American or European company is among the top 10 in Japan. At the same time, Japanese companies, which for the most part are not multinational, are now pushing to increase their export markets and to globalize their operations.

The pharmaceutical industry, despite high entry barriers, is not particularly concentrated. No company holds even a 5 percent share of the world market (as of 1991). This should be qualified by the fact that, when disaggregated by therapeutic class, most top-20 pharmaceutical firms have some area of monopolistic or oligopolistic control. In 1987, the 10 largest firms held only 27.6 percent of the world market. The four largest firms in the PMA accounted for only 25 percent of sales in the United States; the top eight for under 50 percent; the top 21 for about 75 percent. There is neither a central product in the pharmaceutical market nor a long-term product leader. Availability of financial resources can serve both to determine existing firms' competitiveness and to bar new entrants, including biotechnology companies. Because comparatively few drugs maintain large market shares for extended periods, companies must aggressively market approved products and develop innovative new ones in order to compete. Competition is both static and dynamic. In the static sense, competition is based on product differentiation, but not price. Dynamic competition is derived from R&D and new product introduction. Market share, which changes with new product introduction, is another measure of competition.[37]

Under growing health care cost constraints in the United States, Canada and Europe, these competitive factors are changing. Many in the biotechnology industry are sure that the basic underlying science can reduce human suffering — and do it cost effectively. In virtually every major debilitating disease, the cost of failure to prevent morbidity — the cost of custodial care, lost productivity, lost taxes, lost life — far exceeds the cost of successful therapy. Studies show that diseases, such as arthritis, cost the United States some $50 billion a year. And as the population ages, the drain of such "hidden" costs will grow, and grow rapidly. Clearly, therapies that address the root cause of such diseases would be cost-effective. The hope of biotechnology is to find solutions for society's most pressing health care needs — at a pace that will yield cost savings to finance still further discovery.

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37 Ibid.

2.2.2 The Agriculture Industry

Agricultural biotechnology (agbio) is diffusing into applications which aim to improve the productivity of crops and livestock, assist in the achievement of environmental protection and sustainability, and increase the amount, variety and value of foods produced. In the area of crop improvement, agbio aims to:

- increase productivity (e.g., with more productive transgenic crop varieties);
- confer disease protection (using rDNA methods to transfer disease-resistant genes into target crops);
- confer insect protection (using rDNA methods to transfer the genes which produce proteins that discourage insects from eating plants into target crops);
- confer drought tolerance (using rDNA methods to transfer the genes from drought-resistant plants to target crops);
- confer uniform ripening (through rDNA methods to control the ripening process in fruits);
- produce biofertilizers and plant nutrition (e.g., using soil microbes to facilitate nutrient uptake);
- produce biopesticides, biofungicides and bioherbicides; and
- open alternative markets (e.g., altering agricultural crops to produce fuels, lubricants, plastics and other industrial applications).[38]

The principles of biotechnology can be applied to enhance livestock health and productivity by raising disease resistance, improving veterinary diagnostics, enhancing hardiness, increasing feed efficiency, improving stock genetics, increasing the yield and nutritional quality of meat, eggs and milk, and solving animal health problems. By replacing traditional breeding and selection programs for large animals, biotechnology can greatly accelerate the speed at which desirable characteristics can be selected into a targeted population. This effort will yield benefits in growth and production, animal health, veterinary vaccines, improved animal products (e.g., through modification of the fat content in milk and meat), and through the use of animals as bioreactors (to produce high volumes of drugs and nutrients at relatively low operating costs). In this latter respect, transgenic sheep have produced antitrypsin for the treatment of people at high risk of developing emphysema. Transgenic cows will be able to produce lactoferrin, a substance found in breast milk and a good source of iron and of natural immunity. Scientists have isolated the

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[38] "Agricultural biotechnology for the 21st century: explore exciting opportunities in North America." Biotech '95 videoconference material presented at the BIO '95 conference in San Francisco, California, 1995.

human gene for tPA, a substance which promotes the free circulation of blood (see Chapter 3), and transferred it to a sheep embryo. The milk from the resulting ewe provides a new source of tPA for the treatment of heart attacks.[39]

Biotechnology is involved in the animal feed industry. Beyond the use of physiologically active compounds [viz., rDNA-produced bovine somatotropin (BST)], transgenic microbes and plants have been found to improve efficiencies in the production of nutrients and other feed additives of interest to the livestock industry (viz., the efficiency of feed conversion in ruminant animals). Probiotics are being developed with animal feed applications (e.g., to create a gastro-intestinal environment conducive to favourable bacteria). Biotechnology can be used to design improved pastures, provide better silage inoculum and engineer improved digestive function directly into livestock.

Biotechnology is making significant contributions in the diagnostic field. Diagnostic technologies — useful on the farm, in the factory and on the supermarket shelf — include immunologically based tests, genetically based probes and bioelectronically based sensors. Typical applications include veterinary diagnostics, the detection of pesticide residues on plants and animals, early identification of pathogens and spoilage organisms in food and feed, and process control and monitoring during the manufacture of food products.

Zero tolerance standards for food-borne pathogens in critical raw materials and finished products require the precision monitoring which DNA probes can provide. In addition, these diagnostic kits are portable and work faster than traditional culture methods. These new diagnostic methods can detect food-borne bacteria, test rapidly for total microbial load, predict microbial quality and the shelf life of foods, provide rapid diagnostic methods for drug residures, diseases, pollutants and contaminants, and monitor industrial bioprocesses.[40]

Aquaculture, the farming of aquatic organisms, is a major global industry valued at over US$30 billion per year. Production is increasing by 10 percent per year, and the value of production by 12 percent. World supply from capture fisheries peaked in 1989 at 90 million tonnes and is now in slow decline. Aquaculture is addressing the gap between declining supplies from capture fisheries and growing demand. North America produces only 3 percent of the world aquaculture production. (Asia produces about 85 percent). However, the sustainability of aquaculture depends on learning how to control bacterial and viral infective diseases in farm fisheries and on the production of aquatic animal feed. Biotechnology is addressing these production problems on several fronts, including nutrition, health, growth promotion, genetics, product quality, waste management, environmental monitoring and remediation. Currently, rDNA growth hormones, the technology for growth enhancement, biosensors to monitor the freshness of fish products and fish health diagnostics are all commercially available.[41]

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39 Ibid

40 Ibid

41 Ibid

Agricultural biotechnology can reduce the impact of agriculture on the environment and conserve soil and other resources on which agricultural sustainability depends. Typically, for example, bioherbicides and bioinsecticides are much more environmentally benign than chemical pesticides. Biological pesticides are more specific, affecting only the target pest, and are readily biodegradable. These products are discussed more fully below.

In addition, biotechnology can contribute to the more efficient management of agricultural and other wastes, by assisting in their conversion to feed, fuel or other uses. Biotechnology can develop improved microorganisms for the treatment of human waste, for composting agricultural, industrial and municipal organic wastes, and for treating industrial effluents, wastewater, contaminated soil and petroleum spills. Phytase, a biotechnological feed enzyme, reduces phosporus levels in manure and has found wide acceptance where intensive livestock operations cause pollution problems. Methane production from cattle, which has global impacts on climate, can also be reduced through applications of feed biotechnology. Enzyme-based detergents are another value-added product from the agricultural waste stream. Biotechnology also contributes to the broader use of biodegradable agricultural products such as the use of vegetable oils for lubricants, fuels and detergents.[42]

Perhaps the most important promise of agbio lies in its potential to feed the world. Climate or other environmental limitations prevent many countries from being self-sufficient in their food production. Biotechnology may make it possible to "customize" the genetic make-up of crop plants so they can grow in exceptionally dry or wet, hot or cold climates. Other potential benefits include increased crop yield, less use of chemical pesticides and improved nutritional content. Agbio, therefore, promises not only agricultural and economic benefits but also environmental benefits from less reliance on chemical pesticides and herbicides. And its application in forestry, to produce modified pulp trees for use in paper production, will allow manufacturers to use less water and other natural resources, and to produce less waste from the production stream, while producing higher quality materials.

Biotechnology food products currently entering the U.S. and Canadian markets include (U.S. entry dates in brackets) cotton plants requiring less chemical herbicides (late 1995); high-quality, fresh market tomatoes modified to ripen on the vine (1994); rapeseed plants which produce more than 40 percent laureate oil, a high-quality raw material for soaps, detergents and cocoa butter replacement fats (1995); modified tomatoes with superior colour, taste and texture and a 10 to 14 day shelf life (April, 1993) and rDNA tomatoes with a 30 to 40 day shelflife (March, 1995;); rDNA-produced chymosin used in about 60 percent of all hard cheese products; and rDNA-produced bovine somatotropin to induce 10 to 15 percent greater milk production in cows (used by farmers with herds representing 30 percent of all U.S. cows.[43]

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[42] Ibid

[43] Biotechnology Industry Organization. *Agricultural Biotechnology: The future of the world's food supply.* BIO: Washington, DC, 1995.

Agbio products expected in the U.S. and Canadian markets within six years include:

- salmon which grow from egg to market size (8 to 10 lb.) in 12 to 18 months versus three years with conventional fish breeding;
- rDNA cotton fibre with enhanced fibre performance, reduced dye-shop pollution and improved textile manufacturing efficiency;
- rDNA tomatoes, raspberries, strawberries, bananas and pineapples with delayed ripening and longer lasting features;
- cotton plants requiring less chemical insecticide to achieve greater crop yield;
- rapeseed plants genetically modified to provide high-quality raw materials such as
    - stearate, an oil requiring no hydrogenation and used for cocoa butter replacement fats,
    - myristate for soaps and personal care products,
    - medium chain fatty acids for high-performance lubricants, nutritional formulas and high-energy foods, and
    - lower saturates for healthier liquid salads and cooking oil;
- corn modified to have natural protection against the European corn borer, a devastating insect pest; and
- higher starch content potatoes requiring less oil for processing and, therefore, of economic benefit for the processor.[44]

Biopesticides based on natural agents such as microorganisms and fatty acid compounds are toxic only to targeted pests (such as the European corn borer) and do not harm humans, animals, fish, birds and beneficial insects. Because they can act in unique ways, they can control pest populations that have developed tolerance to chemical pesticides. Bioherbicides and biofungicides are designed in the same way to combat targeted weed plants and organisms without harming the rest of the environment. Products that will soon be available include:

- herbicides compatible with herbicide-resistant corn, cotton, sugar beets, soybean and canola/oilseed;
- cockroach bait non-toxic to users, pets and the environment; and
- biofungicide to control bacterial plant diseases.

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44 Ibid

Biopesticides currently on the U.S. market include:

- products effective against the Colorado potato beetle, the tobacco budworm, cotton bollworm, soybean looper, velvetbean caterpillar, green clover worm, gypsy moth, spruce budworm, European corn borer and leaf-eating caterpillar pests;

- biofungicides that protect against powdery mildew (used on strawberries, grapes, tomatoes, cucurbits and ornamentals) and post-harvest rot;

- bioinsecticides that combat the beet armyworm, cabbage looper, diamondback moth, cabbage webworm and imported cabbageworm;

- biofungicides for use on roofs, buildings, sidewalks and greenhouses to resist moss, algae and lichen; and

- a bacterial organism called Bacillus thuringiensis (Bt) which produces proteins toxic to certain insects, and harmless to other animals and people. Bt technology is being deployed to produce a line of biotoxin and fatty acid-based products for field testing in the poultry and livestock industries, in crop production (tobacco, corn, cotton, potato and soybean crops) and for ornamental plants and turf.[45]

Conventional or rDNA-derived enzymes are used successfully in commercial food preparation and industrial manufacturing. As highly efficient catalysts, enzymes reduce manufacturing costs, improve product quality and reduce waste problems. They are biodegradable and replace synthetic chemicals that may harm workers or the environment. Manufacturing applications are discussed in the biochemical industry sub-section following. In the commercial food industry, chymosin, described earlier, is one success story. Here, enzymes are used in baking, cheesemaking, starch processing, fruit juice extraction, wine making, edible oil processing, meat tenderizing, brewing and animal feed areas.[46]

According to forecasts by Lindemann Consulting:

- The global revenues for transgenic plant varieties (soybean, cotton, sugar beet, tomato, canola, horticulture) will exceed $2 billion by the year 2000 and $8 billion by 2005 when transgenic plant varieties will hold more than a 50 percent market share in all the major crops harvested by developed countries.

- By 2000, seed sales of insect-resistant transgenic corn, cotton, soybean and tobacco will reach a combined worth of $1 billion. Insect-resistant transgenic tomato and

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45 Ibid

46 Ibid

potato seeds will generate sales of $150 million.

- By 1999, the U.S. market for high oleic acid canola will reach at least $200 million (the total edible oil market in the United States is now $5 billion).[47]

Table 2.4

Projected Markets for Transgenic Seeds, Plants and Produce: 2000 and 2005 (US$M)

	2000		2005	
Crop	U.S.	World	U.S.	World
Total seed:	$626	$1,170	$4,005	$7,330
Canola	1	5	10	160
Corn	25	50	1,300	2,000
Cotton	100	150	180	250
Potato	50	100	180	350
Rice	0	0	75	400
Soybean	400	600	800	960
Sugar beet	0	165	30	350
Tomato	30	50	30	60
Wheat	0	0	400	800
Other seed	20	50	1,000	2,000
Cut flowers	150	500	190	640
Produce	450	450	650	850
Total	**$1,226**	**$2,120**	**$4,845**	**$8,820**

Source: Lindemann Consulting.

If these forecasts are realized, policy makers should note that Canada could experience a displacement phenomenon away from naturally occurring lifeforms where it currently enjoys a competitive advantage.

Our survey found:

- Canadian biotechnology sales totalled $50.6 million (US$37 million) in 1993 for recombinant agricultural and horticultural products or about 1.7 percent of total world sales, and $539.1 million (US$405 million) in the same year for natural lifeform agricultural and horticultural biotech products.

- Total Canadian agricultural biotechnology product sales grew rapidly at an average 17 percent per year over the 1989 to 1993 period.

- Exports of naturally occurring agri-products increased steadily from 1989 to 1993 at 8 percent per year, while recombinant agri-product exports remained steady in the $43 million to $48 million (US$32 million to US$35 million) range.

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[47] Coombs, J. and P.N. Campbell. *Biotechnology Worldwide.* Newbury Berkshire, UK: CPL Press, Science House, June 1991.

Table 2.5 provides estimates of animal vaccine markets by type of biotechnology product. Table 2.6 provides U.S. and world microbial product market estimates for the years 1995 and 2000. These microbial products are classified in either the agricultural or environmental biotechnology sectors. Our study could not generate the level of detail required to distinguish the value of Canadian sales in these areas from total agricultural and environmental biotechnology sales.

Table 2.5

Markets for Selected Veterinary Vaccines Developed Using Biotechnology (US $M)

Vaccine	Market size
Feline leukemia	$50
Pseudorabies	12
Bovine rhinotracheitis	30
Poultry viruses	350
Mycoplasma pneumoniae	30
Swine scours	40
Canine heartworm	85
Flea	200
Cattle grub	12
Dog and cat sterility	50
Cattle/sheep roundworm	100
Immunological enhancement of growth hormone	100
Total	**$1,059**

Source: Lindemann Consulting.

Table 2.6

Summary of Markets for Microbial Products: 1995 and 2000 (US$M)

Microbial Products	1995		2000	
	U.S.	World	U.S.	World
Microbial pesticides	$100-180	$250-400	$500-1,000	$1,000-2,000
Rhizobium inoculants	15	30	20	50
Mycorrhizae	5	10-30	5	10-30
PGPRs	3-5	5-10	3-5	5-10
Frost protection	0-5	0-10	0-5	0-10
Silage inoculants	50-70	100-120	70-100	150-200
Total	**$173-280**	**$395-600**	**$598-1,135**	**$1,215-2,300**

Source: D.Glass Associates, Inc.

Table 2.7 provides revenue, R&D spending and profits for U.S. agbiotech firms which can be compared to the performance of the U.S. pesticide and seed companies.

Table 2.7

1993 Revenue, R&D Spending and Profits for U.S. Agbiotech Firms, and Pesticide and Seed Companies

Companies	Revenue ($M)	R&D ($M)	R&D/Employee ($K/empl))	Profit/Loss ($M)
Agbiotech Companies				
Agridyne Technologies	$1.2	$4.3	$91.8	-$5.3
Biotechnica Int'l (7/93)	23.1	0.0	0.0	-5.4
Calgene (6/93)	27.2	10.3	27.5	-25.2
Crop Genetics Int'l	3.3	6.4	91.5	-8.5
Delta & Pine Land (8/93)	66.1	3.8	NC	8.3
DNA Plant Tech.	10.3	10.4	19.1	-33.9
Ecogen	19.1	5.3	32.5	-11.9
Ecoscience (6/93)	4.3	7.0	58.2	-9.4
Embrex	2.2	3.8	42.8	-7.3
Escagenetics (3/93)	0.8	4.4	69.9	-5.8
Idexx Labs.	93.1	6.9	18.4	9.7
Mycogen	120.5	16.9	19.9	-43.2
Neogen (5/93)	7.6	1.0	8.9	-0.5
Ringer (9/93)	15.2	1.3	23.9	-2.4
Syntro (9/93)	6.0	3.1	52.6	-0.0
Total	**$400.2**	**$84.9**	**NA**	**-$1,40.8**
Pesticide and Seed Companies				
American Cyanamid	$4,277	$595.6	$22.4	-$163.7
Dekalb Genetics (8/93)	292	43.9	19.6	3.1
Dow Chemical	18,060	1,256.0	22.7	644.0
DuPont	32,732	1,132.0	9.9	566.0
FMC	3,754	149.2	7.2	41.0
Monsanto	7,902	626.0	20.9	494.0
Pioneer Hi-Bred (8/93)	1,343	105.2	21.9	137.5
Zeneca Group	6,627	766.8	24.8	650.1
Total	**$74,987**	**$4,674.8**	**NA**	**$2,371.9**

Notes:
Results are for the fiscal year ending December 1993, except as noted.
NA means not available.
NC means no change.

Source: Standard & Poor's Compustat Services (Englewood, CO) as reprinted in *Bio/Technology*, Vol.12, August 1994, pp.755-756.

- The global enzyme market (for all uses, not just agri-food) has been estimated as follows:
  - for food applications, $225 million in 1991 and $475 million by 2000;
  - as detergent additives, $200 million in 1991 and $300 million by 2000;
  - for diagnostics, $40 million in 1991 and $125 million by 2000; and

- as biocatalysts, $40 million in 1991 and $150 million by 2000.[48]

2.2.3 The Biochemical Industry

Biotechnology has a number of applications to chemical production. Clearly, it will be used to improve production of biochemicals currently produced using fermentation, such as industrial enzymes. In addition, there are limited applications to the production of fine chemicals now being produced synthetically. There are more limited applications to the synthesis of complex chemicals and to the production of bulk chemicals. Most of these applications will be developed to improve production processes used by major chemical companies. They will probably be introduced without the fanfare that has accompanied other biotechnology developments. The use of biotechnology in the chemical industry is publicized only when a problem arises.[49]

Chemical firms are beginning to invest in these obvious applications. Currently, there is limited investment in the production of bulk chemicals and fuels using biotechnology due to the relatively low price of oil and recent restructuring in the chemical industry.

Several Canadian active-ingredient manufacturers are industrial suppliers to the Canadian-based pharmaceutical industry (predominantly generic drug manufacturers). These companies are based in Ontario (around Toronto) and Quebec (around Montreal). Their existence is relevant to prospects for the growth of a Canadian-based biopharmaceutical industry.

Amino acids are used mainly as food additives and animal feed supplements, but they have other uses as well. The sweetener Aspartame is made from two amino acids: asparic acid and phenylalanine. The food additive monosodium glutamate (MSG) is probably the best known amino acid. The amino acids world market for amino acids was estimated at US$800 million in 1991, and was growing at 3 percent annually, although the U.S. market was growing slowly or not at all.

Enzymes are biochemical catalysts. Of the approximately 18 commercially available in bulk, five are most important. These are amylases, which produce simple sugars from more complex ones and are used in the starch industry; bacterial proteases, which digest protein and are used in detergents; papain, for dehazing beer and tenderizing meat; glucose isomerase, for making high-fructose corn syrup; and rennin and chymosin, both used in cheese making.[50] A variety of enzymes have been developed for other industrial uses. For

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[48] U.S. Congress, Office of Technology Assessment. *Biotechnology in a Global Economy.* OTA-BA-494, Washington, DC: U.S. Government Printing Office, October 1991.

[49] Ibid

[50] Greenshields, R. (ed.). *Resources and applications of biotechnology: the new wave.* New York: Stockton Press, 1988.

example, one bacteria-derived enzyme, cellulase, which breaks down cellulose, the molecular base of cotton, has been used to soften new blue jeans as an alternative to harsh stone washing. [51]

The world market for industrial enzymes was valued at US$900 million in 1993. The food industry — primarily starch conversion, dairy products and food and drink — accounted for half of the commercial enzymes consumed. Uses include glucose isomerase in the production of high-fructose corn sweeteners for the drink industry, recombinant chymosin rennin for cheese making (itself a $140 million market) and the maltogenic amylase, an anti-staling agent which is replacing chemical monoglycerides in bread formulations.[52]

Although more than 50 percent of industrially produced enzymes (according to both Novo Nordisk and Gist-Brocades) have been genetically engineered to improve yields through gene amplification, non-food use has not progressed as far as was expected, with the exception of the detergent industry. There, substances such as proteases, cellulases, amylases and lipases are used.

Table 2.8

Worldwide Sales of Industrial Enzymes by Market ($M)

Type of Enzyme	1993 Sales ($)	Market Share (%)
Food	450	50.0
Detergents	270	30.0
Diagnostics	70	7.8
Fine chemicals	45	5.0
Other[a]	65	7.2
Total	**$900**	**100%**

Notes: [a] Includes medical, paper (pulp and waste treatment), textiles, agricultural (silage treatment and animal feed) and leather industries.

Source: See Footnote 35.

Major suppliers of commercial industrial enzymes include companies such as Alko Ltd. (Finland); Amano Pharmaceutical (Japan); Bayer AG (Germany); Cuhor (Finland); Gist-Brocades (Netherlands); Genencor International (United States); Novo Nordisk (Denmark); and Solvay & Cle SA (Belgium), which recently acquired the Miles Inc. (United States) line from Bayer; the Biocatalysts Ltd. unit acquired by Shell Ventures (U.K.); and Nagase & Co.

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51 Lubove, S. "Enzyme-eaten jeans." *Forbes*, Vol. 146, No. 10, October 29, 1990, pp. 140-141.

52 Stroh, W.H. "Trends in use of industrial bioprocessing enzymes for the 21st century." *Genetic Engineering News*, September 15, 1994, pp. 10-12.

(Japan).[53]

Current limitations on the use of enzymes in industry are mainly due to the cost of isolating the enzymes from natural sources, their instability, their activity within a narrow temperature and pH range and to the fact that many enzymes function in aqueous systems, which leads to difficulties in the separation of reaction products. The problems these limitations pose for large-scale enzyme applications in industrial processes are being overcome.

The European Commission has focused on programs in both bioprocess engineering and enzyme R&D, designed to commercialize industrial biotechnology and to increase the competitiveness of European biotechnology by supporting collaborative agreements among universities, research institutes and private industry. Key enzyme-related projects include the production of novel biocatalysts, particularly lipases/phospholipases, extremophile microorganisms and their secondary metabolites, such as oligo- and polysaccharides, and chiral intermediates; and the sequencing of host cells, including Bacillus subtils, Saccharomyces cerevisiae and Arabidopsis thaliann. The main industry participants include Gist-Brocades (Netherlands), Henkel (Germany), Novo Nordisk and the joint holding company, Unilever (United Kingdom and the Netherlands).[54]

The majority of industrial enzymes are hydrolytic. However, in the case of near-anhydrous synthesis, a hydrolytic enzyme works in reverse by combining molecules to make a larger one. For example, subtilisin, whose natural function is protein hydrolysis, readily catalyzes acylation of sugars in organic solvents. Enzymes able to function in two phases (e.g., lipases at a water–oil interface) are being developed and will influence specialty chemical and pharmaceutical manufacturing.

In the course of evolution, microorganisms have adapted to life under extreme environmental conditions. Some grow well at temperatures near the freezing point of water (psychrophiles); others thrive at temperatures close to the boiling point of water (thermophiles). Still others are optimally adapted to low (1.2) or high (9.1) pH, or are dependent on a high salinity in their environment (thalophiles). Extremophiles, as factories for the formation of novel enzymes and low molecular weight secondary metabolites, such as oligo- and polysaccharides, particularly those enhanced by protein-engineered functions, could transform R&D projects into viable products.

Bacterial polysaccharides already have numerous applications in the cosmetics, food ingredient (gums), paper, oil recovery, textile and pharmaceutical industries. However, numerous technical obstacles limit development of novel genetically improved biopolymers. Unlike proteins, natural polymers are not created by a genetic blueprint, but rather by a synthesis pathway in the organism. These pathways range from a minimum of 10 steps up to 100 steps.

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53 Ibid

54 Ibid

By using rDNA techniques, different pathways can be created or blocked with engineered enzymes using metabolic engineering. This creates entirely new biosynthetic pathways or polymer assembly lines. These new metabolic pathways could be used to produce greater quantities of a particular polymer or to design novel polymers with unique physical and functional properties. Novel biopolymer products are not expected before the turn of the century. However, new enzymes derived from extremophile organisms are already emerging in the marketplace.

The main biocatalysts on the market encompass a limited range of products. Fine organic chemicals are still made mainly by classical synthetic routes. In most cases due to the age of the plant, the existing process operates in a fully depreciated plant. Any new manufacturing technique would need to provide major, if not dramatic, cost advantages on a full cost basis, if it is to be adopted. Product development time has been reduced by about 80 percent to one to two years, thanks to advances in recombinant expression systems and protein engineering. However, considering the cost of developing custom enzymes, there is another obstacle — the end product market is tiny. Consider that the total global requirement for cephalosporin antibiotics is 1,200 tonnes with consequent low requirements for enzymes used in making the key intermediates. Since most types of cephalosporin will go off-patent in the 1990s, lower-cost generic cephalosporins might be encouraged with consequent opportunities for enzyme innovators.[55]

The major producers of commercial enzymes are Novo Nordisk (Denmark) with about 40 percent of the market, and Gist-Brocades (Belgium) with about 20 percent, followed by Rohm (Germany), Miles (United States) and Hansens (Netherlands).[56] The current market for industrial enzymes is over US$650 million per year.[57] In 1991, the global enzyme market was segmented as follows:

- 40 percent for the starch industry;
- 30 percent for the dairy industry;
- 5 percent for the baking industry; and
- 25 percent for brewing and others.[58]

Because industrial enzymes are intermediate biotechnology inputs in the manufacture of final (and often non-biotech) products, our survey could not identify Canadian sales nor the extent to which they are produced domestically or imported.

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55 Ibid

56 Greenshields, R. (ed.). *Resources and applications of biotechnology: the new wave.* New York: Stockton Press, 1988.

57 U.S. Congress, Office of Technology Assessment. *Biotechnology in a Global Economy.* OTA-BA-494, Washington, DC: U.S. Government Printing Office, October 1991.

58 Decision Resources, Inc. "Collected biotechnology market data." *Spectrum Biotechnology Review,* 1993.

Another report[59] estimated:

- The total EC market for enzymes in 1991 was $313 million with expected growth to $416 million by 1995. The three largest enzyme groups are:
  - proteases used in the dairy and detergent industries ($141 million and $187 million in 1991 and 1995 respectively);
  - carbohydrases used in starch conversion, alcoholic beverages and detergents ($63 million and $83 million); and
  - lipases, used in detergents and cheese products ($31 million and $41 million).

- The largest European end-user industry for enzymes is the non-food category, which includes paper coatings, footwear, textiles and agriculture, but not medical applications. The non-food sector in the EC had a $91 million enzyme market in 1991 and is forecast to top $128 million in 1995.

- Medical and diagnostic uses of enzymes are expected to double from $7 million in 1991 to $14 million in 1995. The largest national markets in 1991 were Germany ($83 million), France ($58 million) and the United Kingdom ($45 million). Most European markets are expected to have 20 percent growth over the 1991 to 1995 period, except for Germany which can anticipate its industrial enzyme market to double.

- In 1990, the first genetically engineered food ingredient (chymosin from E. coli E-12) was produced by Pfizer and approved by the U.S. Food and Drug Administration (FDA) for use as a replacement for rennin for milk coagulation in cheesemaking. Also in 1990, the first genetically engineered baking yeast was produced by Gist-Brocades and approved for use in the United Kingdom. In 1991, a genetically engineered maltogenic amylase from B. subtilis was marketed by Novo Nordisk Bioindustry for use as an anti-staling agent in baking.

Biotechnology can be used to improve the yield of an enzyme through the transfer of the gene encoding the enzyme to a microorganism capable of producing the enzyme in larger amounts. Novo Nordisk researchers were able to create a detergent additive using a fat-digesting enzyme made from a fungus genetically encoded to produce the enzyme in higher quantities. The detergent containing this enzyme was first introduced in Japan. Biotechnology can also contribute to the field of industrial enzymes through genetic encoding of enzymes with altered characteristics (e.g., more stable in harsh solvents, more heat resistant or reactive with different substrates such as degrading the proteins found in

59 "Industrial enzymes: a boon industry in Europe?" *Biotechnology News*, Vol. 12, No. 17, 1992, p. 3.

blood or food stains).[60]

In the very long run, biotechnology may have a major impact in shifting the production of fuel and bulk chemicals from reliance on non-renewable resources, such as oil, to renewable resources such as biomass. Currently, there is not much industrial interest in such applications because continuing low world oil prices have discouraged investment in altematives, and because the worldwide chemical industry underwent restructuring during the 1980s. As the major oil companies increased their bulk chemical production, the chemical firms decreased their share of the bulk chemical market and increased their interests in the production of specialty chemicals, pharmaceuticals and agricultural products. The industry's restructuring was a strategic response to worldwide pressures (viz., low oil prices, recessions, increasing competition and new costs in the form of environmental protection regulations, particularly in the United States).

Chemical companies reduced operations in bulk chemicals, generally retaining production of chemicals in which they were the market leader or in which they had a price advantage based on proprietary technology. Other operations were sold.

Between 1981 and 1986, Dow sold more than $1.8 billion in assets and wrote off most of its oil and gas business. Bulk, low-value chemicals once provided 61 percent of Monsanto's profits; the proportion shrank to 35 percent in a four-year period. American Cyanamid once consisted of four roughly equal segments: medical, agricultural, chemical and consumer products. By 1987, medical and agricultural products made up about 75 percent to 80 percent of its business.

Also during the 1980s:

- American firms, which had dominated bulk chemical production in Europe during the 1950s and 1960s, gradually withdrew, selling their assets to local firms.
- Chemical firms expanded into the two sectors — pharmaceuticals and specialty chemicals — which continued to be quite profitable and recession-resistant. Most of this expansion came through acquisition.
- Major producers of agricultural chemicals diversified into seed production.
- Chemical firms have expanded their interests in advanced materials and instrumentation.

Restructuring has been successful, in that industry profits recovered from the slump of the early 1980s. More recently, however, recession and rising oil prices have hurt the industry once again.

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[60] U.S. Congress, Office of Technology Assessment. *Biotechnology in a Global Economy.* OTA-BA-494, Washington, DC: U.S. Government Printing Office, October 1991.

There are many examples of chemical industry restructuring and resulting investment in research-intensive fields. Since 1985, Monsanto, the St. Louis-based chemical firm, has shut down or sold more than 20 businesses that were largely producers of high-volume, low value-added chemicals. At the same time, they have acquired firms producing specialty products, including pharmaceuticals, food additives and detergent chemicals. Similarly, Dow's managers decided in 1978 to cut back on bulk chemicals and extend the firm's interests in specialty chemicals and related high-value areas. In 1981, Dow acquired Merrill, a U.S. pharmaceutical firm and, in 1984, it acquired an 84 percent interest in a small Japanese pharmaceutical firm, Funai Pharmaceuticals Co., Ltd. Dow has also expanded its interests in household cleaning products, polymers and advanced ceramics. DuPont recently joined with Merck to form a new pharmaceutical firm. It has also joined with DNA Plant Technology in its FreshWorld venture, selling branded vegetable produce. Rohm & Haas has invested in agricultural biotechnology firms in the United States and Belgium.

Restructuring in Europe and Japan had similar results. The major European chemical firms have redistributed their assets and, like American firms, have invested heavily in R&D-intensive products. For example, Hoechst, a large German chemical manufacturer, purchased Celanese in 1986, acquiring its advanced facilities for the production of pharmaceuticals, which represent 17 percent of its world sales. Hoechst was also one of the earliest big investors in biotechnology, providing $70 million to Massachusetts General Hospital in 1980 in exchange for the right to license research results and to send its own scientists for training. The British firm ICI has developed its presence in agricultural products through the acquisition of seed companies and by expanding its existing research in plant biology.

In addition to acquiring pharmaceutical and agricultural firms, some American and European chemical companies have invested heavily in internal research in the life sciences. Among these are: Monsanto, DuPont, Lubrizol, Royal Dutch-Shell, ICI and the French companies, Elf-Aquitaine and Rhone-Poulenc. The petrochemical company, Lubrizol, acquired the plant biotechnology firm, Agrigenetics in 1988.

Although outright acquisitions of biotechnology firms are rare, other relationships between chemical companies and small biotechnology firms are quite common. DuPont, for example, has R&D, marketing and licensing agreements with several small firms, including American Bionetics, Applied BioTechnology, BioTechnology General Corp., Cellular Products, Cistron, Genofit SA, Molecular Biosystems, and Synergen. American Cyanamid has agreements with BioTechnology General Corp., BioProbe, Cytogen Corp., Molecular Genetics, Inc. and Quadra Logic Technologies in Vancouver.

European and Japanese firms have also contracted with or invested in many small U.S. firms specializing in biotechnology, but they have not fostered the development of similar small firms in Europe or Japan. A recent study showed that chemical companies provided 63 percent of the research funds spent by the top 15 plant biotechnology firms in 1989. The leading investors were Monsanto (United States), Enimont (Italy), DuPont (United States), Sandoz (Switzerland) and ICI (United Kingdom).

Global restructuring of the chemical industry in the 1980s has resulted in investment in high-value-added products such as pharmaceuticals, agrochemicals and other specialty chemicals. As firms reduce investments in the production of low-value added chemicals, it becomes less likely that research in biotechnology applications for biomass-based production will be funded by the private sector.[61]

The chemical industry's greatest impact on the use of biotechnology is likely to have little to do with industrial chemical production per se. Indeed, its greatest impact may be the result of the industry's expanding investment in pharmaceuticals and agriculture. This investment has taken the form of increased in-house research and links with smaller research-intensive firms.[62]

2.2.4 The Environment Industry

According to John Gibbons, Science Advisor to President Clinton, the market for environmental biotechnologies is expected to grow to $300 billion by the year 2000.

Table 2.9 shows estimates of Canadian, U.S. and European markets for bioremediation in 1992 and 2000.

Table 2.9

Projected Demand for Bioremediation (US$M)

Market	1992	2000
United States	$100-125	300-550
Canada	15-25	25-50
Europe	80-115	325-600
Total	**$195-265**	**$650-1,200**

Source: D. Glass Associates, Inc.

- For 1992, our survey estimated environmental sales at $36.6 million (US$27 million) or 10 percent to 14 percent of these combined markets. The 1993 Canadian sales totalled $66.7 million (US$49 million) which already is at the top end of the D. Glass Canadian projections for the year 2000.

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61 Ibid

62 Ibid

A recent U.S. study projected:

- The American bioremediation market will be between $158 million and $186 million in 1993. This market is forecast to total $2.2 billion to $2.8 billion by the year 2000.

- By 2000, underground storage tank (UST) remediation will account for $1.5 billion of the total. UST work is expected to peak in the mid-1990s and tail off by 2000.

The U.S. study defined the bioremediation market as the application of biological processes to the remediation of land-based sites — UST sites and hazardous sites such as Superfund, Department of Defense, Department of Energy, *Resource of Conservation and Recovery Act* (RCRA), and other non-marine sites. Highlights of the environmental sector include:

- Over 90 percent of the 1993 economic activity in the environmental sector in Canada and the other markets was paid for consulting, engineering and remediation services. The U.S. study estimated this activity in 1993 at between $150 million and $175 million.

- The balance of activity in this sector in the United States was spent on the production of microbes for bioremediation ($6 million to $7 million) and bioreactors ($2 million to $4 million).

- The Canadian market is growing much faster than the U.S. market with a tenfold increase between 1989 and 1993. The U.S. market more than doubled.

- Currently, economic activity is concentrated in the areas of *in situ* applications and biostimulation of indigenous microbial populations.

- The U.S. engineering consulting and remediation services field is dominated by about 30 companies, with the top 10 companies representing about 60 percent to 70 percent of the market in 1993.

- The U.S. microbe market is dominated by four major microbe producers.

- The equipment market is fragmented; many consulting/engineering and remediation companies also design and assemble their own equipment.

- Most Canadian environmental companies are small (70 percent have 25 or fewer employees). This is also true in the U.S. market where 40 percent of the surveyed consulting/engineering and remediation companies, 90 percent of the microbe producers and 60 percent of the specialized equipment manufacturers had fewer

than 50 employees on staff.[63]

The U.S. study noted that the number of consulting/engineering and remediation companies entering the bioremediation market was significant during recent years.

- Only 15 percent of the companies surveyed reported offering bioremediation services before 1985.

- An estimated five to 10 companies had completed more than 20 bioremediation projects by 1988; five years later, the number of companies with 20 completed projects was estimated to be between 30 and 35. However, any cross-sectional survey including our own will fail to pick up business failures particularly in the relatively new field of environmental biotechnology. These estimates should, therefore, be treated with caution.

The U.S. bioremediation market became more competitive during the period studied. The combination of changing customer requirements, the increasing number of service companies and the recent recession has driven profitability down. Profitability from bioremediation for consulting/engineering and remediation companies, as measured by gross profit margins, was reported as much lower than five years ago. This parallels a trend in the environmental remediation market and is true as well for Canadian companies whose representatives have reported tougher, more intransigent markets across the country now than in the 1980s.

The U.S. study also found that:

- Market conditions are expected to keep pressure on profit margins for these companies, creating significant business challenges and opportunities.

- Bioremediation's share of the remediation market is forecast to increase during the next 10 years for five reasons:

  - education of regulators, customers and environmental consultants;
  - an increasing number of successfully completed bioremediation projects;
  - continuing improvements in bioremediation technology and its application to a broader range of contaminants;
  - cost reduction efforts by service suppliers; and
  - a regulatory environment which is more favourably disposed to the use of bioremediation.

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[63] Devine, Katherine. "Bioremediation market forecast at $2 billion to $3 billion." *Biotreatment News*, October 1993, pp. 4-6.

These conclusions also mirror the statements of Canadian environmental firm representatives.

The U.S. study identified market opportunities in technology development and implementation including the development of bioventing (air injected above the water table) and biosparging (air injected below the water table) applications; the use of centralized bioremediation facilities for petroleum-contaminated soil; biofilters; and significant improvements in the cost effectiveness of bioremediation and the ability to hold margin with more competitive prices.

Additionally, the U.S. study found (as in Canada) that a few companies were pursuing genetically engineered microbes. In this country, 1.6 percent of all 1993 firm level biotechnology economic activity was in the recombinant environmental field. However, this activity only translated into $0.3 million of licensed sales activity clearly indicating it is still at the R&D stage in Canada.

Other opportunities may include applying bioremediation technology to industrial plant waste streams, selling technology or pursuing foreign markets. Pursuing export sales is another promising opportunity for Canadian environmental firms. Exports have sprung to life since 1990 and now account for $20.2 million or about 30 percent of all economic activity in this sector. Even more promising is the fact that this export growth turned around a small environmental sector trade imbalance situation (running at about -$3.4 million before 1991) into a healthy trade surplus of $14.8 million in 1993.

In the near term, it is unlikely that there will be much growth in sales for rDNA technologies. Nevertheless, there has been a recent report of an application for regulatory approval by the Environmental Protection Agency (EPA) for a recombinant product to bioremediate polychlorinated biphenyls (PCBs). Given impressive Canadian sales growth of natural environmental biotechnologies averaging 80 percent per year (1989 to 1993), this industry can be expected to be a major economic performer for the country over the next decade and beyond. The Canadian environmental biotechnology industry's export business also reinforces our conclusion about the potential for this industry.

2.2.5 Biopolymers

Biopolymers are often just one of many components in a product. The addition of a biopolymer to a product may improve the function of that product and, therefore, improve its value. Improving or adding functions to a product will be the major role of most biopolymers. The ability to develop novel biopolymers may provide a company with the opportunity to improve a product's competitive position by improving its functionality.[64]

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64 "Cleaner, greener biocides in the 1990's." *Biotech Forum Europe,* Vol. 9, October 1992, p. 610.

The biocompatible and bioactive properties of biopolymers will be important in the development of new medical products. A new generation of pharmaceuticals and devices may develop based on the unique properties of biopolymers. Some of these products, such as advanced wound dressings or coatings for implants, may result in improved patient care, shorter hospital stays and decreased health care costs.

Additional areas into which biopolymeric usage may expand include consumer tastes, bacterial cellulose and functional foods/nutraceuticals. Consumers are currently demanding foods that contain fewer calories from fats, and these demands are driving the development of substances that can mimic or replace fats in food processing applications. A number of synthetic products are under development (e.g., Proctor & Gamble's Olestra and Kraft General Food's Trailblazer) yet naturally derived products are having a greater impact because they undergo less regulatory scrutiny and, thus, enter markets quickly. Consumer tastes will continue to drive new markets for biopolymers, and this area deserves particular attention.

Advances in production processes for bacterial cellulose promise to increase the use of this material by reducing its cost and making the material more readily available. Both ICI and Weyerhauser have developed production methods that employ special strains of bacteria and that improve yields and production economics. These new production processes could lead to the commercial use of bacterial cellulose in areas other than high-value, premium-priced specialty applications.

Functional foods/nutraceuticals are foods and food-derived substances that prevent disease or restore health. Oat bran is a functional food — it reportedly can lower blood cholesterol levels. A key area to monitor with respect to functional foods is the difference between how regions or countries classify functional foods and the level of market exclusivity they give companies for pursuing R&D. For example, Japan and the European Community have already instituted procedures for either approving product labelling or granting companies market exclusivity for nutraceuticals. In the United States and Canada, interest in nutraceuticals is growing, but incentives to introduce nutraceuticals do not exist. The HPB and FDA both require substantial data proving efficacy before allowing a company to make health-related claims about a product (food or drug).

The 1992 global market for biopolymers was estimated at US$1.2 billion and consisted of food processing ($0.6 billion), biomedical uses ($0.2 billion), oil field biopolymers ($0.16 billion) and other applications ($0.24 billion). This market is forecast to expand to $1.6 billion by 1997 and to $2.5 billion by 2002. It is expected to comprise: food processing ($1 billion), biomedical uses ($0.8 billion), oil field biopolymers ($0.3 billion), cosmetics ($0.2 billion), other industrial uses ($0.1 billion) and cell culture adjuvants ($0.1 billion).

Table 2.10 shows current biopolymer functions and uses.[65]

Table 2.10

Biopolymer Functions and Uses

Function	FP	P	TP	D	C	OIA	Biopolymers in Use
Dispersing, suspending agent	X	X	X			X	Xanthan, alginates
Stabilizer	X			X			Tragacanth, gelatin, guar, xanthan
Thickener	X		X		X		Carrageenan, guar, tragacanth, xanthan
Gellant	X	X				X	Alginate, carrageenan
Binder	X	X	X	X	X		Starch, carrageenan
Foam former	X						Alginates, gelatin
Humectant	X						Casein, carrageenan
Lubricant		X			X	X	Hyaluronic acid
Flocculent	X					X	Chitin
Adhesive	X	X	X			X	Animal glues, polyphenolic protein
Biocompatibility promoter		X			X		Chitin, polyhydroxybutyrate, hyaluronic acid

Notes: FP = Food processing; P = Pharmaceuticals; TP = Textile papers; D = Detergents; C = Cosmetics; OIA = Other industrial applications.

Source: SRI International (1992).

2.2.6 Country-Specific Information on Biotechnology

Information on biotechnology activity in the other G-7 countries (United States, United Kingdom, France, Germany, Italy and Japan), other selected countries (Australia, Austria, Belgium, other East Asian countries and the Netherlands) and some important biotechnology firms in those countries follows.[66]

United States

Comparative information on U.S. biotechnology is found throughout all chapters of this report and in tables 2.2, 2.3, 2.4, 2.6, 2.7 and 2.9 of this chapter. In this section, we look at components of U.S. industrial strategy for biotechnology including policies favouring U.S. nationals and U.S.-based firms. The following discussion is based on recent congressional testimony by Roger Herdman, Director of the U.S. Office of Technology Assessment which

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65 "Cleaner, greener biocides in the 1990's." *Biotech Forum Europe,* Vol. 9, October 1992, p. 610.

66 Biotechnology Industry Organization. *Agricultural Biotechnology: The future of the world's food supply.* BIO: Washington, DC, 1995.; Herdman, R.C. "The Biotechnology Industry." U.S. Office of Technology Assessment Testimony before the Joint Economic Committee. OTA, Washington, June 24, 1994.

provides a succinct overview for health care biotechnology products.[67]

In some 15 years, over 1,000 small to medium-sized U.S. NBFs have been started to develop or manufacture pharmaceuticals for human use. About 200 of these firms are public companies. In fiscal years 1992 and 1993, these firms raised more than $11.5 billion in new external capital financing. (This figure does not include in-house biotechnology R&D by established pharmaceutical corporations.) Most of this investment took place in the United States although the sources of the investment capital are global. Herdman believes this is because the United States remains the pre-eminent site of biotechnology research and manufacture in the world today.

U.S. federal government support for biomedical R&D, technology transfer policies and strong IP protection have created an environment conducive to discovery and commercialization of new therapeutic advances. Serious efforts have been made by the FDA to rationalize the regulatory process and reduce delays in approvals for biologics. Most important, widespread health insurance for prescription drugs in the United States and other industrialized countries has provided a dependable market for biotechnology drugs relatively unencumbered by patients' ability to pay. Together, these factors have made investment in research on new biotechnology-based health care products less costly, less risky and, potentially, more financially rewarding. More private sector investment has also been stimulated than would otherwise have happened.

U.S. government funding of life science research over the last half century has created a research infrastructure whose size, scope and productivity is unparalleled in the world. In 1993, the government spent almost $12 billion on health R&D — roughly 39 percent of all U.S. health R&D. Although this spending grew almost 90 percent in constant dollars over the previous 10 years, it was even more important at the time when rDNA and related technologies were first being developed. For example, in 1983, federal funding was 50 percent of all health R&D, with industry providing another 39 percent.

The U.S. government has been largely responsible for developing the talented cadre of scientists who make the significant biological discoveries in government, academia and industry. Over several decades, the National Institutes of Health (NIH) has provided training awards to some 1,000 to 1,300 doctoral students and post-doctoral fellows each year. Other federal agencies, such as the Department of Education and the National Science Foundation, have provided educational support for science at the secondary, undergraduate and graduate levels. Herdman notes that many students and fellows have worked in their professors' laboratories on NIH-supported research grants, extending that government's training support well beyond explicit training programs.

The U.S. government has developed successful technology transfer (TT) policies during the last 15 years to move federally sponsored research findings from the laboratory to the marketplace. In academia, the most important of these policies was the *Bayh-Dole Patent*

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[67] Herdman, R.C. "The Biotechnology Industry." U.S. Office of Technology Assessment Testimony before the Joint Economic Committee. OTA, Washington, June 24, 1994.

and Trademark Act of 1980 (Public Law 96-517). This law gave universities, non-profit organizations and small businesses the intellectual property rights to inventions from federally sponsored research. In return, it required these institutions to share any royalty income from patents with the scientists responsible for the invention. The law also required universities to make a good faith effort to seek patents on discoveries and to look for licensees for those patents. The holders of patents must also give licensing preference to small businesses and companies who agree to manufacture any products resulting from the licence in the United States.

The impact of Bayh-Dole on the commercialization of federally funded biomedical research has been extraordinary.

- A recent survey of 260 academic institutions revealed that over 1,000 licences and options were executed in 1992, and over 5,000 active licences were in place at that time. Today, some research universities with active biomedical research units generate millions of dollars per year in licensing fees and royalties from private companies.

Federal laboratories, particularly at the NIH, carry out important basic and applied life sciences research. To date, Herdman claims that virtually every treatment available for HIV/AIDS, its opportunistic infections or cancer has involved important research in NIH laboratories. An NIH laboratory supported the discovery and development of the first successful drug to treat Gaucher's Disease, a potentially life threatening and crippling inherited disorder. NIH isolated the crucial enzyme missing in patients with this disease, contracted with Genzyme Corp. to produce research quantities of the enzyme, and planned and paid for the pivotal clinical trials supporting its FDA approval. Genzyme applied for orphan drug status for the drug (see sections 6.3.2 and 6.4 of this report) and developed it for the market. Today, Genzyme has exclusive rights to sell the drug in the United States.

In the late 1970s and 1980s, Congress passed a series of laws to facilitate the TT process including making the TT and patenting essential duties of federal laboratories. The most important of these was the *Federal Technology Transfer Act* of 1986 (Public Law 99-502). It required agencies to share at least 15 percent of royalties from licensed inventions with the inventing scientists. The law also permits the establishment of formal co-operative R&D agreements (CRADAs) in which a federal laboratory and a non-federal party (usually a private firm) both provide resources for collaborative research. The U.S. government can agree in advance to grant exclusive licences to the collaborating partner on any invention resulting from the CRADA.

- The number of patent applications filed by the U.S. Public Health Service (PHS) has rapidly increased (from 100 in 1987, to 160 in 1988, 230 in 1989 and 240 in 1990). In addition, the number of licence agreements issued on patents held by PHS showed a steady and dramatic increase during the 1980s (rising from seven in 1980 to an average of 50 or 60 per year from 1989 to 1991).

CRADAs have also proven to be a popular form of TT, especially with smaller firms. For several years in the late 1980s and early 1990s, there were approximately 110 CRADAs in existence at NIH at any one time. The last two years have seen increases in the number of new CRADAs, with a 37 percent increase in 1993 alone for a total of 206 agreements in operation.

U.S. patent law is generally regarded as the most inventor-friendly statute in the world in terms of patentable subject matter.

- In recent years, biotechnology patent filings have been increasing at an average annual growth rate of about 15 percent, compared with about 7 percent for other kinds of patents. In 1993, almost 4 percent of all patents issued by the U.S. Patent and Trademark Office (USPTO) were biotechnology products.

Herdman notes that product patents can be difficult to obtain for biotechnology drugs because if just a small amount of the product was isolated or identified previously, the product is unpatentable since it is considered prior art. In contrast, synthetic pharmaceuticals almost always consist of new active ingredients that are patentable. Consequently, biotechnology firms often depend on "process" patents to protect their intellectual property. He cites recent federal appellate decisions, especially *in re Durden* in 1985, which have increased the difficulties in obtaining a process patent involving biotechniques. He also notes the surge of litigation in this new area of patent law, which has created some uncertainty about the strength of biotechnology patents. Congress is attempting to assist in this area, and legislative initiatives on biotechnology process patents are currently proceeding through both houses of Congress (e.g., US Bill H.R. 587, a bill to amend title 35, United States Code, with respect to patents on biotechnological processes).

Even when the conventional patent system presents problems for biotechnology, many biotechnology drugs have access to effective patent protection through other government-sanctioned grants of market exclusivity. The *Orphan Drug Act* of 1983 (Public Law 97-414) which is described in Sect.6.3.2, provides seven years of exclusive U.S. marketing rights to the first firm receiving FDA approval to market a drug for any indication that affects less than 200,000 people in the United States. Of the 27 biotechnology drugs approved for marketing in the United States to date, 15 have orphan status for at least one indication.

Herdman also provides an important insight about the impact of the FDA's stringent regulations for the introduction of new biologics on the effective patent protection of biotechnology drugs once their patent or orphan drug exclusivities expire. Unlike chemical drugs which can usually be easily and reliably copied, biotechnology drugs cannot be easily separated from the production process. In other words, small variations in methods of producing a biotechnology product can lead to unexpected changes in the product, and those changes can be detected only with proper testing for safety and efficacy. Consequently, the FDA requires clinical testing for "generic copies" of biotechnology products even after patents have expired on the original product. The cost of conducting such research is high and will probably discourage copies from entering the market. He

notes that, before 1984 when U.S. law was changed to make approval of generic copies of chemical drugs more feasible, many chemical-based drugs had no competitors for many years after their patents expired. This insight has profound implications for the development of Canada's generic drug industry.

The importance of intellectual property protection to the stimulation of private investment in biotechnology research is illustrated by recent investments in human genomic research. Since its inception in 1988, the Human Genome Project (HGP) has been largely a publicly funded effort — in the United States, Canada and elsewhere. The U.S. HGP is an estimated 15-year $3 billion initiative to identify the location and composition of the 50,000 to 100,000 human genes. The project has been undertaken with the expectation that enhanced knowledge about genetic disorders, increased understanding of gene-environment interactions and improved genetic diagnoses can advance therapies for the 5,000 or so currently recognized human genetic conditions. Herdman notes the proliferation of private investment over the last two years in entities specifically intended to conduct and develop large-scale human genome research (Table 2.11).

Table 2.11

U.S. Companies Involved in Commercializing the Human Genome

Company	Research Plan	Reported Funding (major sources as of 5/94)	Year Founded
Collaborative Research	Use of semi-automated mapping, positional cloning and semi-automatic multiplex sequencing to locate genes for therapeutic development.	$3.3M (Federal funding and NASDAQ investors)	1961[a]
Darwin Molecular	Focus on rapid DNA sequencing to screen and amplify potential pharmaceuticals.	Estimated $50M (VC[b]; P. Allen and W. Gates)	1993
Human Genome Sciences	Selling or licensing genetic information from the Institute for Genomic Research to pharmaceutical companies.	$156M (SmithKline Beecham ($125M) and NASDAQ initial public offering)	1992
Incyte Pharmaceuticals	High speed sequencing to find genes and corresponding proteins for drug development, bioinformatics.	$13M (American Stock Exchange initial public offering)	1994
Mercator Genetics	Use of positional cloning or "reverse genetics" to develop common disease therapeutics.	Unknown	1992
Millenium Pharmaceuticals	Use of genome mismatch scanning to isolate genes related to diseases and target them for drug development.	$70M (Hoffman-LaRoche)	1993
Myriad Genetics	Focus on development of diagnostic tests for disease genes.	Estimates of $12M (VC; Eli Lilly)	1992
Sequana Therapeutics	Use of positional cloning to find and isolate genes for diagnostic and therapeutic purposes.	Estimates of $5M (VC)	1993

Notes:

[a] Collaborative Research began significant funding of human genetics research in the early 1980s, and then further expanded and reoriented its focus toward genomics, as outined in the research plan above, in 1993.

[B] VC = venture capital funding.

Source: Office of Technology Assessment, 1994, based on R.M. Cook-Deegan, "Survey of Genome Science Corporations," contractor document prepared for the Office of Technology Assessment, U.S. Congress, January 1994; G. Bylinsky, "Genetics: The Money Rush is On," *Fortune*, May 30, 1994; and L. Fisher, "The Investment Allure of Biotechnology Stocks," *New York Times*, December 3, 1993.

Two NBFs, Human Genome Sciences (HGS) and Incyte Pharmaceuticals, had raised over $40 million in separate IPOs by late 1993. HGS was founded with $70 million in venture capital funds by the NIH researcher who devised an automated gene sequencing program and was responsible for identifying the chemical sequences of genes at NIH. These private investments are the direct result of investors' expectations that the gene sequencing results will generate revenue as a research data base and lead to patentable diagnostics and therapies.

In contrast to the law governing the FDA's review of chemical drugs, there is no statutory limit on the amount of time FDA reviewers may take to complete their review of a biotechnology drug. Nevertheless, Herdman notes that the FDA takes an average six fewer months to review biotechnology-based drugs than it requires to review other drugs.[68] This finding may be due to the practice of the FDA of giving drug applications a priority according to their contributions to therapy; or it may be an artifact, based on the relatively small number of biotech drugs which had undergone review by 1994, and may not incorporate the effect of other biotech drug applications as yet unapproved.

In another emerging biotechnology-based area, gene therapy, an additional layer of regulation of research protocols has been established. (Gene therapy involves the addition of a gene to human cells in order to induce an organism to perform certain functions.) Ethical concerns about the implications of gene therapy have led to the development of a review of clinical research protocols not only by the FDA, but also by the NIH Recombinant DNA Advisory Committee (NIH-RAC). Mindful of the potential for delay and undue burdens associated with these added review layers, the NIH-RAC recently developed categories of gene therapy protocols that could be eligible for accelerated review or even be exempted from full NIH-RAC inspection. These recommendations are awaiting action by the NIH director, but their development reflects the sensitivity of the research community to the burdens posed by unnecessary regulation of biotechnology and a willingness to reduce such burdens whenever possible.

Herdman notes that, for about 85 percent of the American populace, health insurance covers the costs of prescription drugs, when dispensed as part of a hospital stay or requiring administration by a physician. About 75 percent have insurance for drugs prescribed by doctors to outpatients. About 50 percent of people 65 years of age and over have outpatient prescription drug insurance, but all elderly Americans are covered for drugs when dispensed in hospitals under the Medicare benefits. This insurance reduces the sensitivity of patients to drug prices. Additionally, most U.S. physicians still prescribe on the basis of medical benefits, and not on relative price, which explains why pharmaceutical companies spend

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68 Ibid

20 percent to 25 percent of sales to advertise and promote their products to doctors.

The emergence of biotechnology-based pharmaceuticals was aided by the price-insensitive nature of the U.S. health care marketplace. This market is beginning to change, however. Health insurers are injecting more price sensitivity into prescribing and dispensing decisions. This trend has been called "managed care pharmacy" (MCP). A whole new industry of companies that manage the prescription drug benefits for U.S. employers and health insurers has sprung up in the last five years or so. When close substitutes exist on the market, these MCPs use various means to induce doctors to prescribe, pharmacists to dispense and patients to demand the lower-cost alternatives.

Today, many U.S. private insurance drug plans have adopted the generic substitution approach of Canadian provincial formularies. Even when there is no generic copy of a specific compound, close therapeutic competitors may exist. Table 2.12, for example, shows the number of distinct compounds available in the United States in seven narrow cardiovascular categories. Pharmaceutical benefit managers are attempting to force price competition among these close competing alternatives by developing formularies — lists of preferred drugs — and encouraging or requiring the prescribing of drugs in the formulary.

Table 2.12

Number of Unique Compounds Available in the United States in Selected Cardiovascular Categories, 1993

	Number of Unique Compounds
Adrenergic Blockers	6
Adrenergic Stimulators	4
Alpha/Beta Adrenergic Blockers	2
ACE Inhibitors	8
Beta Blockers	11
Calcium Channel Blockers	13
Diuretics	17

Source: Physician's Desk Reference, 47th edition, 1993. Appears in Ref. 29.

This phenomenon is forcing pharmaceutical companies to compete on the basis of price as well as on quality. However, Herdman believes that MCPs are less likely to dampen the prices of new biotechnology drugs to the extent that they represent real advances in treatment or in "breakthrough" drugs and have no close therapeutic competitors. For such unique products, the only lever available to MCPs is to require prior approval before dispensing specific drugs. Approvals would be issued only for approved indications or to persuade doctors to prescribe expensive drugs more conservatively.

However, when strong intellectual property protection for new biotechnology products is combined with a guaranteed market by third-party payers, rising health care costs become an issue. Herdman raises the question of the limits to U.S. society's willingness to pay for technological advances made possible by investment in health R&D. This is the issue at the

heart of the current debate on U.S. health care reform. How much R&D is enough, and how will consumers signal investors about the desired kinds and amounts of R&D? To date, the signals to the U.S. biotechnology industry have been that any therapeutic advance — even modest gains — will be accepted in the medical market place at almost any price.

Recent proposals for a U.S. federal government advisory body to review the "reasonableness" of prices of new "breakthrough" drugs have met with vigorous opposition from representatives of the biotechnology industry who argue that the uncertainty caused by such supervision would dampen investment in new drugs. A similar dilemma faces federal research agencies whose discoveries are transferred to private companies for development and marketing. Because the federal government is both a purchaser of health care products (through Medicare, Medicaid and other programs) and a funder of research that can lead to those products, the PHS has stated its interest in seeing that the price of commercial products based on exclusive PHS licences be commensurate with the "extent of public involvement in the product and the health and safety needs of the public." In its policy governing the granting of exclusive licences, including those resulting from CRADAs, PHS has adopted a fair pricing clause. However, the U.S. Office of Technology Assessment (OTA) has concluded that NIH currently has no way to implement this clause. Implementation would requireexpertise in accounting and economics, and access to detailed audit data throughout the R&D process.

The biotechnology and pharmaceutical industries have argued that the fair pricing clause would discourage firms from collaborating with NIH because it would introduce a new element of uncertainty into the research process. The fair pricing clause dramatically points out the potential conflict that can arise between two important U.S. government policy goals: the desire to use U.S. R&D investment as an engine for economic growth and advances in the treatment of disease, and the need to control health care costs and insure value for health care expenditures. At some point, Herdman states, policy makers and the public will need to face the reality of trade-offs in the health care sectors. Decisions must be and will be made concerning how much health care and medical technology is worth paying for.

The U.S. Biotechnology Industry Organization (BIO) recently launched an initiative with Congress to effect regulatory reform of the FDA for the U.S. biotechnology industry through consideration and adoption of certain amendments to the *Federal Food, Drug and Cosmetic Act* and the *Public Health Service Act.*[69] The BIO amendments have several purposes including:

- improve health care through the rapid approval of safe and effective new biotechnology-derived therapies and vaccines;

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[69] Biotechnology Industry Organization (BIO): *A Draft Bill to amend the Federal Food, Drug and Cosmetic Act and the Public Health Service Act to update laws relating to biotechnology and for other purposes.* 12th draft, BIO, Washington, DC, April 5, 1995.

- reduce development costs by over 25 percent through the elimination of excessive and unnecessary regulation of biotechnology products;

- privatize certain FDA functions; and

- provide regulatory relief to the U.S. biotechnology industry to enhance human health, promote economic growth and improve international competitiveness, while assuring the public that biotechnology products are safe and effective.

The BIO draft bill clearly articulates the U.S. biotechnology industry's perspective on the issues raised by Herdman's congressional testimony.

The United Kingdom

The United Kingdom has a historical reputation for excellence in science, and much of the fundamental innovative research forming the basis of biotechnology today was carried out in U.K. academic and research establishments. In fact, the major discoveries concerning DNA structure and the formation of hybridomas leading to monoclonal antibodies as well as the basic principles behind genetic fingerprinting were made in the United Kingdom. However, the country has not been able to translate easily these early basic discoveries into a strong biotechnology industry. The reasons are twofold: the reliance of academic and research institutes on the perceived prestige of basic science and the reliance of U.K. manufacturing on established technologies and its reluctance to adapt to newer methods.

Recent trends by the government to privatize services and reduce public spending have had a profound impact on industry, the universities and public sector research. As a result, there has been a shift from the position in the past where the strong science base was maintained mainly by public sector support to one of increasing dependence on the pooling of public and private sector resources in support of "precompetitive" research in higher education institutes. The objective of government has been to increase co-ordination between research councils and government bodies, and between academia and industry.

In the United Kingdom, as in other countries, the present biotechnology industry has four major components:

- traditional fermentation businesses (ethanol, organic acid and antibiotic fermentations);
- large multinationals with biotechnology subsidiaries or departments;
- start-up companies formed around new technologies; and
- support companies (providing venture capital, information, consultancy, equipment, reagents, etc.).

In the early 1980s, some 30 independent biotechnology companies, and another 20 funded through venture capital and started by academics, were developing a range of products using either the new techniques of rDNA and hybridoma technology or new methods of waste treatment, enzyme production, biosensors, plant propagation, embryo transfer, blood products, enhanced oil production or algal culture. Large multinational subsidiaries were engaged in a similar range of activities, as well as others in single cell protein, bioethanol production, biopesticides and microbial polymers. These activities reflected the previous decade's problems (higher energy prices, shortage of animal feed protein) as well as the need by smaller companies to develop products inexpensively and rapidly (thus avoiding the pharmaceutical product area) and without uncertainties (associated, for instance, with transgenic plant development).

Major U.K. biotechnology companies in 1991 included:

- ABM-Sturge (organic acids, enzymes, gums, fine chemicals) formed in 1988;
- Agricultural Genetics Co. Ltd. (plant breeding and inoculations);
- Agricultural Technology (based on investments by banks and venture capital firms, and with over 200 staff involved in areas of plant breeding, diagnostics and veterinary products) which has grown by acquisition of other companies, such as Premier Breeders and Landell Mills;
- Amersham International plc (over 3,000 staff, sales of £189 million in 1989 in diagnostics, reagents and enzymes for genetic engineering and in particular radioactive compounds);
- Biotal (consultancy and contract research, waste treatment and agricultural inoculants);
- British Biotechnology (biological reagents, DNA probes and pharmaceuticals);
- Cambridge Research Biochemicals (biologically active peptides, antibodies and various kits) and acquired by ICI in 1989;
- Celltech (as above);
- Chemical Design (chemical-modelling software);
- Delta Biotechnology (rDNA therapeutics);
- Enzymatix (enzymes to produce novel phospholipids, as well as producing diagnostics, enzymes, reagents, etc.);

- Farm Gas (anaerobic digestion waste treatment process);
- ICI Diagnostics (with a subsidiary Cellmark Diagnostics which carries out genetic fingerprinting) and had not yet marketed specific products as of 1991;
- Imperial Biotechnology (contract R&D and enzyme producer by fermentation);
- Inveresk Research International (contract research organization);
- Life Science Research (consulting services, toxicology and immunoassay);
- Mercia Diagnostics (producing diagnostics, enzymes and immuno-products);
- Pharmaceutical Proteins (a venture capital funded company established for direct protein synthesis in transgenic animals);
- Photobioreactors (formed through venture capital to produce food and feed products from algae);
- Porton International (formed from pension fund investments and producing pharmaceuticals and diagnostics as well as fermentation equipment);
- Quatro Biosystems (another venture capital supported company producing diagnostic tests and equipment);
- Serono Diagnostics (diagnostics and related products);
- Twyford Plant Laboratories (producing plants by micropropagation);
- Wellcome Biotechnology (a subsidiary of the Wellcome Foundation, over 600 staff involved in all aspects of modern biotechnology); and
- Xenova (supported by venture capital and producing novel pharmaceuticals from microorganisms).

A number of biotechnology companies have been set up or have benefited from regional development programs aimed at attracting industry to lower economic areas of the country.

By 1991, the most noted trend was a move away from the promotion of the image of the independent biotechnology company as the primary corporate activity. Long lead times and a lack of really striking success stories made venture capitalists and other investors more cautious. Hence, companies were now more likely to be described as involved in a specific area such as plant breeding, food, diagnostics, pharmaceuticals, equipment or engineering, and to have a biotechnology component, but not to thrust it forward as the main reason for

existence. The trend has been for industry consolidation, tempered by the changes in European markets and competition between various companies as trade barriers were lowered with the establishment of a common EC market.

France

A co-ordinated policy was put in place by the French government in the early 1980s to develop strong public and private investment in biotechnology. The policy followed identification of certain problems concerning a lack of qualified researchers, the rigidity of research organizations, the lack of collaboration between industry and universities and research institutes, the low investments in research and the lack of knowledge in biotechnology at the managerial level.

By 1987, government funding for biotechnology in the widest sense had risen to 3 billion French francs, with over 1.7 billion going to various research organizations. French industry is also investing about Fr 2 billion annually in such areas as pharmaceuticals (Fr 350 million), fine chemicals (Fr 100 million), agro-industrial activities (Fr 270 million), seed production (Fr 130 million) and other sectors such as environmental protection and wastewater treatment.

Before 1981, French plant biotechnology was poorly developed. Since that time, efforts by a public research organization (Institute for Agriculture and Agro Food Research) and seed companies (Limagrain, Rhone-Poulenc, Sanofi) have reversed the situation. The area of immunology has received attention from the Pasteur Institute, the Institute of Marseille and companies such as Immunotech.

Agriculture is a key priority area for France and much effort has gone into plant and animal production. Sales by the agri-food industry in France exceed US$1 billion and are the country's primary activity.

In health care, the country's public research organization in this area (INSERM, similar to NIH) and private companies are active in therapeutic, diagnostic and vaccine application areas. Pasteur-Merieux is now the leading company in the world for vaccines. Cosmetic companies (l'Oreal and Dior) are active in biotechnology, and others (Generale des Eaux and Lyonnaise des Eaux) are developing biotechnical processes for water treatment.

The large multinational companies (Rhone-Poulenc, Roussel-Uclef, Sanofi, Synthelabo, Roche and Solvey) are mainly involved in fine chemicals and pharmaceuticals. Their products include immunological products, vitamins, antibiotics, food products (e.g., dairy products, flavours, food additives, starch derivatives, bakers yeast and sweeteners), enzymes and alcoholic beverages as well as organic and amino acids (glutamic, aspartic, lysine and methionine) and bacterial polysaccharides.

A number of companies are involved in wastewater treatment using aerobic and anaerobic methods (SGN, Degremeont, OTV). The novel biotechnology companies include Transgene (Strasbourg) which is working in therapeutic and vaccine applications involving genetic engineering, cell lines and hybridomas. Smaller companies include municipal solid waste treatment (Valorga Process), the use of algae (Pronatec), monoclonal antibodies (Clonantec, Flobio, Immunotech, Sorebrio), plant micropropagation (Plantagen), fine chemicals (Neosystems), image analysis (Imstar), embryo transplants (France Embryon), transformation of agricultural products (Biotropic) and biological control (Calliope).

Germany

The federal government recognized the importance of biotechnology early in the 1970s when it began to support the developing field. A performance plan was adopted in 1979 with both a research program and development objectives. The plan recognized the importance to biotechnology of basic research and interdisciplinary co-operation among the sciences related to biology and engineering. By the mid-1980s, three centres for genetic engineering, mainly publicly funded, were established with industry participation. A program to help companies use biotechnological processes and to stimulate the creation of new companies was introduced. Grants were made available for product and process development, and for precompetitive studies in selected areas (e.g., cell culture and cell fusion technologies, enzyme biotechnology and bioprocess engineering). Stimulation to biotechnology development in Germany is provided by learned and scientific societies, and the European Molecular Biology Laboratory (EMBL) funded by 13 European countries and Israel.

Research strategy for the 1990s is laid out in a program entitled *Biotechnology 2000*. The five-year budget (1989 to 1994) for the program was DM 1.7 billion with a focus on:

- methodology (development of new expression systems, automated analysis, improved sequencing techniques, processing systems and biosensors);
- cell biology gene regulation and structure;
- energy;
- protein design;
- neurobiology;
- biological systems;
- plant breeding;
- renewable raw materials;
- industrial recycling (recovery of materials and low waste systems);
- research animals (biotechnical alternatives to the use of research animals);
- biological risk assessment (development of safety measures and standards for contained use and deliberate release); and
- technical assessment (herbicide resistant plants, deliberate release, somatic gene therapy).

Germany recognizes two major areas of biotechnology: the traditional, based on fermentation processes, and the new, based on molecular biology and genetic engineering. Classical biotechnology has a long tradition in Germany in areas of dairy produce, beer and wine. Traditional fermentation includes the production of chemicals and pharmaceuticals (Hoechst and Bayer). Another traditional use of microorganisms is in waste treatment which has been stimulated by environmental legislation. It has led to new sewage treatment installations and new industrial effluent facilities (involving tower-shaped bioreactors and large concrete digesters).

Commercial biotechnology activities in Germany can be divided into three areas. The first includes the many manufacturers of food and beverage products based on fermentation (with brewers such as Lowenbrau and Hofbrau). Second are the large chemical/pharmaceutical companies (including two of the world's largest, Bayer and Hoechst). The actual biotechnical component of these companies is a small portion of their overall activities, and includes production of semi-synthetic penicillins using immobilized cells or enzymes. Merck and Schering are involved in steroid production, Degussa in amino acids, and Rohm and Boehringer-Mannheim in the production of enzymes. The third sector is represented by companies providing services.

German companies have strengths in the design and manufacture of light engineering and electronic equipment including fermenters (Braun), but the number of specialized molecular biology companies is small. Joint commercial ventures between universities and biotech companies are unusual. In contrast to the large research effort, commercial developments in the new biotechnologies have been fairly modest.

Italy

Excluding antibiotics, amino acids, organic acids and yeast, national sales of biotechnology products are expected to grow from US$50 million to US$60 million in 1990 to US$1 billion to US$1.2 billion in 1995.

The top 50 biotechnology companies in Italy account for about 70 percent of commercial activity. Of these, 30 have a staff of less than 20 devoted to biotechnology, five have more than 100, while the remainder have between 100 and 200 employees working on biotechnology.

Major biotechnology companies include:

- Farmitalia Carlo Erba which is part of the Montedison/Erbamont Group with about 200 employees in advanced biotechnology. It is a privately owned Italian company involved in joint ventures with overseas research centres (Cytogen, Imclone, etc.). It is associated with fermentation companies (viz., Antibiotics in Spain and Lark/Erbabiochimica in Italy);

- Gruppo Lepetit, part of the Merrel Dow Pharmaceutical (Dow Chemicals) Group. Originally it was an Italian antibiotics company, with over 100 staff in advanced technology;

- Sclavo, a pharmaceutical firm involved in vaccines. It is part of the Enichem Group (Italian state owned) and DuPont (United States) and has a staff of 130;

- Sorin Biomedica , a privately owned company with 50 staff specializing in diagnostics and biomedical products. It is part of the Fiat Group; and

- Agrimont, part of the Enimont Group (partly private and state owned), and active in agricultural biotechnology, with a staff of over 100.

Commercialization of research in Italy is achieved through self-funding. However, since 1987, the government has had a number of near-market research programs in biotechnology firms, with a total budget of US$250 million through to 1990. Italy suffers from a shortage of venture capital financing, an absence of technology transfer centres, rigid relations between universities and industry, and a lack of incentives to reduce start-up company risks. However, this situation has been changing in the last few years, justifying optimistic forecasts for near-term growth.

Japan

Government agencies and ministries in Japan play a leading role in promoting science and technology advancement. These and other agencies include:

- the Council on Science and Technology which publishes a white paper each year reviewing Japan's R&D activities and proposing various measures to advance both basic and leading edge life science research;

- the Institute of Physical and Chemical Research which supports life science projects, including research related to genes, cell preservation and microorganisms;

- the Research and Development Corporation of Japan , supporting commercialization of new life science technologies;

- the National Institute of Radiological Science, looking at the effects of radiation on living organisms and cancer therapy;

- the Japan Atomic Energy Research Institute which tests manufacturing radioisotopes for medical use; and

- the Environment Agency which supports research endeavours at the National Institute of Environmental Studies and conducts pollution prevention research.

At the ministry level:

- The Ministry of Health and Welfare supports national research institutes (National Institute of Health and the National Cancer Centre) promoting biotechnology-related research.

- The Ministry of Agriculture, Forestry and Fisheries (MAFF) deploys R&D activities to ensure a stable food supply and productivity in its resource industries. MAFF also promotes biotechnology development in the private sector.

- The Ministry of International Trade and Industry (MITI) supports biotechnology development in its various research institutes, as well as in the private sector through a general policy (Research and Development Project of Basic Technology for a Future Industries) and through development of medical and related equipment and apparatus using advanced technology. It works with private industry through another of its agencies, the New Energy and Industrial Technology Development Organization, to promote R&D in energy conversion technology based on biotechnology.

- The Ministry of Construction promotes development of new wastewater treatment systems using biotechnology.

There are several other government organizations also dealing with biotechnology (e.g., the Council for Science and Technology of the Prime Minister's Office, the Science Council of the Ministry of Education, the Industrial Technology Council of MITI, the Bio-orientated Technology Research Advancement Institution, the Adverse Drug Suffering Relief and Research Promotion Fund and the Japan Key Technology Centre).

Development of the biotechnology industry in Japan (using rDNA and cell fusion techniques) has been based on its fermentation industry which uses microorganisms to produce alcohols, amino acids, organic acids and antibiotics. This base enabled diffusion of the technologies into other industrial sectors, including the more obvious pharmaceutical, chemical and food-related industries, as well as the less obvious machine, electric-electronics, petroleum and construction engineering industries. Thus, chemical and food industry companies have commercialized the production of food additives, amino acids and isomerized sugars and, in addition, the food industry has commercialized the production of antibiotics and other pharmaceuticals, monoclonal antibodies, restriction endonucleases, seedlings and so on. The chemical industry has developed biosensors and purification equipment. Supporting industries have conducted activities aimed at the commercialization of bioreactors, equipment for research and production, as well as clean rooms and

wastewater treatment facilities. A wide variety of products are expected to be commercialized by the Japanese biotechnology industry including amino acids, cosmetic ingredients, industrial enzymes, physiologically active substances, antitumor agents and other pharmaceuticals, interferons, thrombolytic agents, interleukins and erythropotein (EPO), as well as monoclonal antibodies, seedlings and microbial pesticides.
Research which is close to commercial development or marketing is, in principle, carried out by private sector funding. The Small Business Finance Corporation has a loan system for funding facilities and operations in order to promote the industrialization of advanced technologies, including biotechnology. Researchers in publicly funded research institutes are not allowed to be involved in biotechnology venture companies.

In agricultural biotechnology, Mitsui Toatsu Chemicals Inc. organized its in-house Plant Biotechnology Research Group in 1982 to work on tissue culture, anther culture and protoplast culture technologies using various crops such as rice, soybeans and tomatoes. In 1985, a very efficient anther culture was established for rice. In 1986, rice protoplast was regenerated using a unique conditioned medium. This success gave the group an opportunity to use new breeding technologies such as cell fusion and rDNA. It also permitted the use of an electroporation method for gene introduction in rice protoplast and to produce transgenic rice. Because of the successes in advanced biotechnologies for rice, a corporate policy of concentrating only on rice breeding was decided on, taking into consideration that rice is the main food crop in Japan and the domestic seed market was estimated to be 30 billion yen (in 1993).[70]

Through the semi-governmental Research Institute of Innovative Technology for the Earth, Japan's Ministry of International Trade and Industry (MITI) is funding research in ways to absorb CO_2 biologically and to produce hydrogen for use as a fuel.[71]

The small scale, high technology dynamics of the fine chemicals segment of the chemical market have led to sufficient growth in Japan to the extent that Japanese products in biotechnology and chiral chemistry may soon be a force in world pharmaceutical and agricultural chemical markets. The fine chemical business has proven to be a tough market for Japan to enter. However, Japanese companies are strong in antibiotic screening and fermentation technologies. Kirin Brewery, an expert in beer fermentation, built a strategic alliance with California-based Amgen because of Amgen's strength in medical science. Most Japanese companies are interested in producing more fine chemical products but their fermentation and biotechnology processes are not very efficient. Consequently, these firms are becoming interested in expensive fine chemicals with high profit margins.[72]

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[70] Kawasugi, T. " Kubota Corp. tackles agricultural problems of the next generation. *Japan 21st (Business Japan)*, Vol. 38, August 1993, p. 39; Shinozawa, T. " Plant biotechnology projects at Mitsui Toatsu Chemicals, Inc." *Japan 21st (Business Japan)*, Vol. 38, August 1993, pp. 40-41.

[71] Normile, D. "Japan funds biotech for global problems." *R&D*, Vol. 35, April 1993, p. 17.

[72] Dambrot, S. "Strength in fine chemicals: Japan moves forward." *Chemical Week*, Vol. 150, April 8, 1992, p. 44

Another study noted that, while Japan began its biotechnology industry by licensing technologies from U.S. and European partners, it has since invested heavily in biotechnology R&D. By 1989, Japanese spending on biotechnology-related research totalled $2 billion, including $70 million by Mitsubishi Kasei Corp., $72 million by Kirin Brewery Co. and $58 million by MITI to sponsor public–private research projects.[73]

Australia

By 1991, there were about 65 biotechnology businesses in Australia (excluding consultants and waste management equipment manufacturers) employing over 1,000 professionals and with R&D investments of A$127 million (US$95 million). Nearly 80 percent of companies were located in the Sydney and Melbourne areas. Some of the leading companies were:

- Burns Philip & Co. Ltd (180 staff);
- Commonwealth Serum Laboratories (175 staff);
- Biotech Australia Pty Ltd (85 staff);
- Institute of Drug Technology Aust Ltd (60 staff); and
- AGEN Biomedical Ltd (47 staff).

Austria

In the mid-1980s, Austria's biotechnology strengths were in the environmental sector together with engineering disciplines related to plant construction. By 1991, there were some 35 active biotechnology companies, 12 in health care and pharmaceuticals, 19 in environmental applications, eight in bioprocess technology and five in agriculture and food.

The Austrian biotechnology companies selling into global markets at that time were:

- Biochemie Kundl GmbH, Tirol, a Sandoz subsidiary producing antibiotics, enzymes, alkaloids and penicillins, and working in genetics, reactor optimization, process kinetic analysis and downstream processing;

- Jungbunzauer AG, Laa/Thaya, a producer of citric acid, zanthan gum and ethanol;

- Vogelbusch GmbH, Vienna, offering plant design and construction for bakers and fodder yeast, ethanol, vinegar and citric acid and wastewater treatment specializing in continuous bioprocessing including seawater desalination;

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[73] Gross, N. "Japanese biotech's overnight evolution." *Business Week*, Issue 3149, March 12, 1990, pp. 69 and 72.

- Bender & Co (Boehringer Ingelheim), Vienna producing human proteins such as interferons and vascular anticoagulants as well as working in gene cloning, an expression system in E. coli and Saccharomyces, and down stream processing);

- MF Andritz AG producing yeast and ethanol including upstream processing and software for process control of yeast pressing and drying as well as wastewater processing, cell culture and bioreactors including various bioprocess systems;

- Astro GmbH, Graz which carries out environmental analyses and produces water processing equipment and bioreactors;

- Waagner Biro AG, Graz-Wien producing a biological wastewater treatment system known as the "biobed" reactor as well as bio air filters;

- AVL, Graz produces optical sensor devices;

- Voest Alpine, Linz involved in general engineering plant construction;

- BIUTEC GmbH, Vienna which carries out R&D in environmental biotechnology; and

- Babcock Industrieanlagen a producer of waste composting plants.

Belgium

Despite the absence of a national biotechnology development program and its small size, Belgium has a surprisingly large number of industries and R&D centres involved in the field, especially in pharmaceutical and agri-food industries.

Human health care products form a major area for development of biotechnology in Belgium. The presence of university research teams with worldwide reputations and the tradition of basic biological and medical research have contributed to this development. Industrial activities include small and medium-sized start-up companies created with public and private venture capital such as Eurogentec, Gamma, Techland, IRE-Celltarg and Innogentics. Large multinational pharmaceutical and chemical companies are active in Belgium as well, viz., Smith Kline Biologicals, with a leading position in vaccines as a result of its launching of the first genetically engineered human vaccine against hepatitis B. Other vaccine developments are under way (e.g., in tropical diseases and AIDS).

Diagnostic products are well represented in Belgium by companies such as IRE-Medgencis (MAb technology and DNA probe), Gamma, Techland, Innogenetics, Hybritech, Eurogenetics and Sopar Biochem. In therapeutic medical applications, active companies include UCB-Bioproducts (synthetic peptides), IRE-Celltarg (drug-vector for anti-cancer

drugs) and Innogenetics (tumor necrosis factor for therapy of gonadal cancers).

A few companies operate in the field of biotechnology applied to animal health. These include: Eurogentec (fish breeding and vaccines), Norden Europe (diagnostics and vaccines), Solvay (vaccines, antibiotics) and Smith Kline Rit (virginiamycine). A successful result of synergy between industry and university is illustrated by the development of a detection kit for B-lactams in milk. It is marketed by UCB-Bioproducts under the name Penzym.

The food industry is probably the oldest user of biotechnological processes but, so far, new scientific developments have had little impact on the traditional fermentation industry. Activities involving immobilized cell systems for the production of beer and the development of new brewing yeast strains have been carried out by Artois-Piedboeuf-Interbrew. In the field of food additives, citric acid is produced by surface fermentation processes (Citrique Belge), while immobilized enzymes are used to produce glucose and fructose syrups (Amylum). Some small companies are working on specific topics. These include Belovo (isolation of lysozyme from egg white) and Sodelac (extraction of lactoperoxydase and lactoferrin). Enzyme production for the food industry is carried out by International Bio-Synthetics, a joint venture between the Royal Dutch-Shell Group and Royal Gist-Brocades.

Academic biotechnology research is actively applied to agriculture in Belgium. At the industrial level, Plant Genetic Systems (PGS), near the University of Ghent, is a world leader in plant engineering. PGS has developed insect-resistant and herbicide-resistant plants. The company has recently announced a new system that prevents pollen development in plants which can be used for production of hybrid seeds.

Biotechnology applied to waste treatment is not well-developed in Belgium. Some academic teams and small companies (Organic Waste Systems, Bioprocessing, Sanotechnics) operate in this area.

East Asian Countries

East Asian governments are working aggressively to promote biotechnology. Japan already has a small biotechnology industry, and Singapore has established the Institute of Molecular Biology to undertake basic research in biotechnology. However, the most likely breeding ground for a strong Asian biotechnology industry is the People's Republic of China, aided and abetted by Hong Kong. China has produced a large number of first-rate biologists who are eager to work despite low salaries. Further, China has a wealth of natural resources, such as herbs, that have become the basis of traditional Chinese medicine. With appropriate genetic manipulation, many of these substances could provide solutions to medical and economic problems endemic to developing nations. Attacking local agricultural and environmental problems may provide even greater opportunities. One successful attack on the local environmental front stems from the recent discovery of a bacterium that breaks down indigo dye — a pollutant from the garment trade that seriously discolours local

waterways.[74]

Hong Kong is determined to become a significant player in biotechnology by starting two institutions: the Biotechnology Research Institute (BRI) for basic research and the Hong Kong Institute of Biotechnology for marketing research. The entrepreneurial thrust is to be a gateway between the West and the East. Hong Kong's connection with China would provide raw materials to screen. Despite the absence of government support, the fact that it is a major financial centre should improve its prospects for developing a local biotechnology industry.[75] For example, BRI is creating a substitute for red blood cells by combining dextran with hemoglobin and other means. The aim is to commercialize the new compound. Scientists at BRI, Chinese University and four other institutions have identified high technology industries offering the best commercial opportunities and least investment costs. Other BRI technologies under development include improvements in laser technology to help prevent heart attacks.[76]

The Netherlands

Through a national technology program, the government provided funding totalling Dfl. 85.4 million (from 1987 to 1989) to subsidize over 150 R&D biotechnology programs with the general policy aim of broadening the industrial base in the Netherlands. The thrust is to strengthen private sector initiatives in biotechnology and to forge linkages between companies and universities and institutes engaged in this research. This should lead to centres of excellence in biotechnology research in areas such as agriculture and environmental protection.

The biotechnology industry in the Netherlands has a strong foundation in traditional areas, such as the food and beverage sector, postwar fermentation products, veterinary vaccines and modern biological products. Its share of the global market of US $90 billion to $100 billion (1988) in these product and sector areas was 7 percent in 1988. More than 90 percent of the market for biotechnology products concerns the food and beverage industries which account for about 20 percent of the industrial production of the Netherlands, 5 percent of its GDP and 17 percent of its exports. The dairy industry produces Dfl. 12 billion of bio-based products and is the world's largest cheese exporter. Potato starch producer AVEBE is the largest in Europe (50 European percent market share) and Gist-Brocades is first in baker's yeast production (world market share 30 percent). Heineken ranks fourth in world beer sales and brews about 7 percent of the world's beer.

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74 Gwynne, P. "The Chinese biotech connection." *Technology Review*, Vol. 95, July 1992, pp. 19-20.

75 Gwynne, P. "As Hong Kong seeks biotech 'gateway' role." *Research Technology Management*, Vol. 36, May/June 1993, pp. 3-4.

76 Goldstein, C. "Hong Kong's life blood." *Far Eastern Economic Review*, Vol. 155, March 5, 1992, p. 74.

The Netherlands Institute for Dairy Research (NIZO) is the central research facility for the dairy industry. NIZO supplies the cheese industry with standardized starter cultures. Unilever is recognized as one of the major innovators because of its development of high tech continuous processing for milk and yogurt fermentation and enzymatic processes to produce several savoury flavours.

The fermentation industry in the Netherlands was developed after World War II by a number of companies. The largest fermentation industry company is Gist-Brocades which is the market leader in beta lactin antibiotics (25 percent world market share). In enzymes, Gist-Brocades, together with its joint venture IBIS, supplies about 30 percent of the world market. Other major fermentation products are lactic acid (CCA biochem with a 50 percent market share) and gluconates by glucona (joint venture between AVEBE and Akzo-chemicals). Akzo-Diosynth and Gist-Brocades hold strong positions in steroid fermentations.

The main stronghold of the Dutch health care sector is veterinary vaccines with Akzo-Intevet and Duphar (a subsidiary of Solvay) among the top five companies of the world. Two state owned enterprises — the National Insitute of Public Health (RIVM) and the Central Veterinary Institute (CDI) — supply the domestic market with a complete line of pediatric vaccines and foot-and-mouth disease vaccines respectively. Duphar is the leading influenza vaccine manufacturer in Europe. In the field of diagnostics, Akzo-Organon Teknika is a major worldwide supplier of diagnostics for blood transfusion services and clinical laboratories. Akzo-Chefaro and Unilever are important producers of over-the-counter pregnancy tests. The new Dutch start-up company, Eurodiagnostics, has made a successful entry into the market of veterinary, human and food diagnostics.

Enzymatic processes were recently introduced in the traditionally modest Dutch fine chemicals industry, among others for optically active amino acids (Dutch State Mines, DSM), followed by large-scale enzymatic production of Aspartame (joint venture with DSM-Tosoh of Japan). IBIS, a joint venture of Gist-Brocades and Shell, aims at stereoscopic chemicals and launched its first new product in 1989. Enzymatically produced bio-esters from vegetable oils (e.g., isopropyl meristate) for lubricants and for personal care products come from Unichema (Unilever).

Environmental biotechnology has become important to Dutch industry as it works to develop cost-effective effluent treatment technologies to overcome the increasing purification duties levied for wastewater treatment over the last two decades. New anaerobic wastewater technologies were pioneered by the universities of Wageningen, Delft and Amsterdam together with the Central Sugar Company CSM (continuous up-flow active sludge reactor) . This was followed by an in-house development at Gist-Brocades of fluidized bed reactors with active sludge immobilized on sand. Anaerobic processes have become the methods of choice for the treatment of a variety of industrial effluents.

These technologies are now commercialized worldwide by Gist-Brocades and Paques and represent 35 percent of the installed technologies for anaerobic wastewater treatment plants globally. Anaerobic digesters for the huge manure surpluses from the country's

bioindustries were piloted for commercialization in the late 1980s. Bio-filtration installations for the treatment of organic vapours from industrial exhaust gases originated from the University of Eindhoven and have been further developed by industries to full commercial scale application in and outside of the Netherlands. The government is providing financial support to a number of engineering firms, agencies and universities to develop processes for microbiological degradation of recalcitrant chemicals in soil.
A number of Dutch multinationals have invested in in-house biotechnology R&D since the early 1980s. This has resulted in many first-to-market products. In the pharmaceutical sector, Akzo Pharma companies developed recombinant antidiarrhea animal vaccines in 1980, live recombinant Aujeszky vaccine for pigs in 1987 and monoclonal pregnancy tests in 1982. In the cheese industry, Gist-Brocades developed recombinant chymosine in 1989; and in the food industry, recombinant baker's yeast in 1990. The pre-commercial developments include recombinant phytase as an enzymatic feed additive to improve natural phosphate conversion in chicken and pig feed (Akzo-Organon). Active research in genetic engineering is focusing on the cheese industry and plant biotechnology. In the work on recombinant lactic acid bacteria for improved cheese ripening and phage resistance, several universities are involved as well as NIZO and industry (Gist-Brocades and Unilever).

Pioneering work in plant biotechnology is done at the University of Leiden (agrobacterium transformation of dicotyls and monocotyls) and the Free University of Amsterdam (colour expression). Innovations in tissue culture for plant propagation have contributed considerably to the development of the country's highly export-oriented flower industries since the 1970s. Mogen and AVEBE had a variety of transgenic plants were near to or in field tests by 1991 (e.g., potatoes resistant to virus, eelworm and phytophetera). Variety improvements in maize by DNA fingerprinting techniques are studied by a consortium of five European companies in a Eureka project including Van der Have, Cobeco and Zelder. Zaadunie focuses its R&D on disease and stress resistance, adaptation to growing conditions and intrinsic product quality. A recently established new biotechnology firm Florigene, is studying biosynthetic routes to pigments in order to modify flower colours. The production of human serum albumine in potatoes has been published and is further studied by Moben and AVEBE. Research on transgenic animals has been initiated by the new biotechnology firm Genfarm within the University of Leiden.

Capital for commercial developments is in ample supply in the Netherlands. It can be produced by private organizations, such as banks, pension funds and venture capital funds, as well as through public organizations. Private organizations specializing in biotechnology are the RABO-Bank Netherland Biotech Venture Fund, Medical & Biotech Fund and, to a lesser extent, Green Partners, Atlas Venture and Euroventures. On the public side, the Netherlands has a number of regional development agencies. Development agencies in the northern provinces of Brabant and Limburg have invested in new biotechnology opportunities.

The government's Ministry of Economic Affairs supports biotechnology development with technical development credits. This could amount to 60 percent of the development costs (excluding research) on the basis of a credit that does not have to be refunded if the project

fails for either technological or commercial grounds. A number of public and private agencies provide additional business assistance.

While the climate for technology transfer from universities to industry has improved considerably, caution is exercised not to become dependent on contract research which is short term and unlikely to lead to innovative basic research. Universities are now protecting new inventions through patent applications before publishing their discoveries. They are also taking shares in start-up companies in exchange for providing expertise (Probicom, University of Groningen; Florigene, Free University of Amsterdam) and participating in the creation of science parks (Groningen, Twente, Leiden, Wageningen and Amsterdam) where new companies can develop their first products in collaboration with university research groups and using university facilities.

While the entrepreneurial culture and tradition in the Netherlands is alive and well, in comparison with the United States, it is quite conservative and allows little room for new approaches and start-ups. As a consequence, Dutch venture financing provides significantly shorter burn rates (and development horizons) than in the United States. Real high profit seeking and high-risk venture capital is quite scarce in the Netherlands leaving many initiatives underfinanced. While a strong market-pull effect could compensate, the small home market does not permit this to take place.

2.3 Factors Affecting the Competitiveness of Canadian Firms

This section examines the importance of various factors to the international competitiveness of Canadian biotechnology firms from the point of view of survey respondents (Table 2.13) and personal interviewees. Interviews were conducted with firm representatives at the most senior level, usually the chief executive, whereas survey respondents were at the middle management level, except for the smallest of firms. The comparison of these perspectives on competitiveness illuminates distinctions between operational issues (the concerns of middle managers) and strategic issues (the responsibility of senior executives). Note that, because of small sample sizes, this analysis cannot distinguish between factors related to location in Canada and to the size and maturity of the biotechnology firm.

For the health care sector, survey respondents listed the factors "availability of trained personnel," "sources of training" and "quality of education" as providing competitive advantages. This suggests that Canadian community colleges and universities are producing sufficient numbers of well-trained science graduates for the current staffing needs of health care biotechnology firms.

However, when the issue of the effect of trained personnel on competitiveness was put to senior health care NBF executives during interviews, they began by ranking international markets in order of importance with the United States ranked first, then Europe, Japan in third spot and then Canada. Market preference is dictated by size, remoteness and difficulty of entry.

Table 2.13

The Importance of Various Factors to the International Competitivenss of Canadian Biotechnology Firms by Sector

Factors Affecting Int'l Competitiveness of Canadian Biotechnology Firms and Their Rating	Firm Classification (%)						
	Health	Agri.	Env't.	Supp.	Res'ch	Res'ce.	Total
Availability of raw materials:							
Advantage	69	100		38	35	85	66
Disadvantage	31		100	62	65		30
Neither						15	4
Average wage rates:							
Advantage	20	24		15	31		16
Disadvantage	54	76	100	76	69	81	74
Neither	26			9		19	10
Quality of education:							
Advantage	68	32	39	65	67	52	57
Disadvantage	32	68	42	35	33	18	36
Neither			19			30	7
Current exchange rates:							
Advantage	43	80	52	48	87	65	58
Disadvantage	57	9	31	48	13	26	36
Neither		11	17	4		9	6
Availability of trained personnel:							
Advantage	47	39	37	34	45	35	41
Disadvantage	39	61	51	55	39	65	50
Neither	14		12	11	16		9
Sources of training:							
Advantage	60	63	36	24	46	36	45
Disadvantage	40	37	64	67	28	42	46
Neither				9	26	22	9
Research centres:							
Advantage	69	78	30	44	50	64	56
Disadvantage	22	22	70	52	50	36	41
Neither	9			4			3
Current regulatory environment:							
Advantage	33	21	32	22	11	27	26
Disadvantage	53	70	62	70	76	64	64
Neither	14	9	6	8	13	9	10

Note:
Respondents were asked to rate the effectiveness of the indicated factors.

While on the surface there appears to be a level playing field between the United States and Canada, health care executives reported a number of obstacles to commercialization in the United States which function like non-tariff barriers. For example, the FDA requires American-based clinical trials and refuses to accept Canadian evidence of safety and efficacy. In some cases, the U.S. government also insists on domestic manufacturing facilities as a precondition for sales. This issue is complicated by additional hidden costs, such as those facing a Canadian NBF seeking to attract U.S. expertise in the form of a low exchange rate and higher local taxes. A few of these obstacles to export growth are being

addressed at the provincial level. For example, the Quebec government reportedly provides taxation relief for foreign nationals working in firms in designated sectors (viz., biotechnology). This mirrors taxation schemes of foreign governments seeking to induce export growth. For example, the Taiwanese government exempts foreign nationals from personal taxation in industrial firms exporting more than 50 percent of their products.

Health care survey respondents rated "current exchange rates" as a disadvantage. There is a push–pull phenomenon with exchange rates. For health care firms in the early stages of commercialization, a lower exchange rate is a disadvantage. For firms with developed products and/or technologies competing in foreign markets (viz., agricultural firms), it is an advantage. The response underlines the developmental stage of Canadian health care biotechnology. Except for health care firm respondents, current exchange rates were viewed as an advantage by others (suppliers being evenly divided).

While "research centres" were viewed as a competitive advantage for health care, agricultural and resource-based firms, they were perceived as a disadvantage for environmental and supplier firms. The availability of research support by governments, universities, industry and hospitals (for health care firms) is undoubtedly responsible for much of this advantage. However, the environmental biotechnology industry has suffered a lack of comparable support. This opinion was supported by interviews with a broad range of spokespersons in Canadian environmental biotechnology.

The factor "average wage rates" was seen as a competitive disadvantage by all respondents. This reflects the traditional view of management. The issue has risen to prominence for all Canadian firms facing foreign competition.

The constellation of factors — "availability of trained personnel," "quality of education," "sources of training" and "research centres" — all received negative ratings by environmental firm respondents. This sector shows a promising potential to develop an export capability but, as the "third wave" of biotechnology development (behind health care and agriculture), it is emerging in an era of declining public resource availability. Nevertheless, the ingredients for strengthening Canada's international competitiveness in this sector are available across the country in universities, industry associations, in various sizes of consulting/engineering firms and in government itself.

Agricultural sector respondents declared that "sources of training" provided a competitive advantage, but that "availability of trained personnel" and "quality of education" were disadvantages. Training facilities (universities, community colleges or other facilities) may not be meeting the standards required for international competitiveness in agricultural biotechnology. This comment echoes a general finding on Canadian competitiveness (Table 2.1).

The factor "availability of raw materials" was seen as an advantage for health care, agriculture and resource firm respondents, and a disadvantage for environmental, supplier and research firm respondents. The unequivocality of environmental respondents (100 percent saw this factor as a competitive disadvantage) suggests there is a serious issue here.

It is unclear whether it relates to the availability of *specific* raw materials (e.g., microbial inoculants, bioreactors or other process engineering materials) or to the availability of *cheap* raw materials. The overall negative responses from this sector's respondents across most factors warrant a serious examination by government policy makers.

Finally, respondents were unanimous in regarding the "current regulatory environment" as a competitive disadvantage. This response begs the question: is there no way to streamline Canadian biotechnology regulations to promote the industry's development without compromising health and safety standards? In the health care sector, efforts to revamp the HPB regulatory approval process have apparently stalled. Provincial health ministries have added another layer of hurdles to market entry in this country. The same question has been raised during interviews by firm representatives in all sectors.

A recent study identified strict U.S. product liability law (designed to develop safer products and provide manufacturer-based social insurance) as a factor which drives up biotechnology product development costs and reduces competitiveness. In addition, it fails to achieve its policy goals of conferring product safety and inducing manufacturers to provide social insurance against the potential for harm from product use. The study calls for industry-specific change in the application of the U.S. product liability law to improve the environment for the commercialization of biotechnology and to restore global competitiveness to U.S. biotechnology.[77]

In some ways, strict product liability and market preclearance regulations are substitutes. Hence, Canadian firms should consider regulatory costs as well as product liability in assessing the costs of market introduction of their biotech products. Newt Gingrich, the U.S. House Speaker, addressed the recent Bio '95 conference in San Francisco. He proposed privatizing the FDA and creating an insurance system with contributions from biotech companies to cover their product liabilities.

In selected instances, society has recognized the social benefits from lowering regulatory barriers and costs, thereby increasing product liability exposure (e.g., AZT). However, by placing the burden of risk sharing on individual consumers, the demand for biotechnology products may be reduced and the need for a compensatory social insurance mechanism will increase. Given the large developmental costs for biotechnology therapeutics, the issue of increasing product liability exposure needs thoughtful consideration.

2.4 Alternative Competitiveness Strategies for Canadian BiotechnologyFirms

This section explores some successful strategies adopted by Canadian biotechnology firms to enhance their ability to compete in world markets.

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[77] Stovsky, M.D. "Product liability barriers to the commercialization of biotechnology: improving the competitiveness of the U.S. biotechnology industry." *High Technology Law Journal*, Vol. 6, Fall 1991, pp. 363-381.

For health care NBFs, the value-added stages of product development can be identified in order as:

- research
- preclinical testing
- phase 1 clinical trials
- phase 2 clinical trials
- phase 3 clinical trials
- registration/product launch
- license out products
- research products
- small market products
- significant product sales.[78]

Product development proceeds in stages similar to those in the conventional pharmaceutical industry. Each initial stage brings a potential product closer to the market and to producing revenues. After the initial research stage, the potential products, or their components, go through preclinical tests and the three stages of clinical trials. Once the product has passed the clinical trials, it can be registered with a regulatory agency and launched into the market. At this stage, the product can finally start to generate revenue.

A company has some options for generating revenue. It can license out its products for others to manufacture in return for royalties, or it can manufacture products itself. Licensing out products and manufacturing and selling research products, such as monoclonal antibodies, will generate small revenues. Manufacturing and selling small market products, such as diagnostics or therapeutics with limited markets, on the other hand, will generate moderate sales. To reach significant sales, the company must manufacture therapeutic products with a large market potential.

The literature identifies three broad groups of factors leading to successful product development:

- management characteristics
- strategy
- competitive environment.[79]

Firms whose managers have relevant experience, i.e., skills, knowledge and contacts to carry out the work, are more likely to be more successful in new product development than firms whose managers are relatively inexperienced. Also, the management team should be

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[78] Whipp, R., R. Rosenfeld et al. "Understanding strategic change processes." In *Management of Strategic Change.* Edited by A.M. Pettigrew. Oxford: Basil Blackwell, 1988.

[79] Roure, J.B. and M.A. Maidique, "Linking prefunding factors and high technology venture success: an exploratory study." In *Strategic management of technology and innovation.* Edited by R.A. Burgelman and M.A. Maidique. Homewood, IL: Irwin, 1988, pp. 414-423; Weiss, A.R. and P.H. Birnbaum, *Technological infrastructure and the implementation of technological strategies*, Vol. 35, No. 8, 1989, pp. 1014-1026.

relatively complete (with expertise in all functional areas — R&D, regulation, manufacturing and finance). Previous working relationships among the managers are more likely to lead to successful new product development.

Strategy factors which contribute to successful product development relate to:

- the firm's product market strategy (i.e., an overall strategic "vision" and a clear role of product development in corporate strategy);
- a strong market orientation (market research and assessment);
- customer perception of a superior or unique nature of the product(s);
- detailed and systematic planning;
- efficient and fast development work; and
- R&D support systems.

The competitive environment refers to target markets devoid of strong competition and with high growth potential, as well as a network of relationships among producers and users of technology to implement a firm's technology strategy effectively.

A recent study proposed some additional answers to the question of what makes some firms more effective than others in new product development. It used case studies based on five western Canadian health care NBFs.[80] The answers relate to the role of management in product development but go beyond managerial attributes such as experience or skills. The findings suggest that actions and rationales of managers, in particular, shape the outcomes of product innovation. The findings also highlight the importance of context in product development and emphasize the firm's internal environment as well as external elements such as universities and government agencies which extend beyond the competitive environment.

The study finds that a context–content–process model of managerial logics of action provides insight into a firm's effectiveness.

Effective firms, characterized by *innovative logic,* tend to be led by an inventor–entrepreneur (with a raison d'être and power base) who provides stable leadership. This type of manager maintains university collaboration, a market focus (with a large market potential), long-term financing (including R&D) and a complete management team (with expertise in all functional areas — R&D, regulation, manufacturing and finance).

*Ineffective firms,*characterized by *prestige logic*, tend to be led by a non-inventor–entrepreneur who provides unstable leadership. This type of manager seeks government support, lacks focus (is content with small market products), maintains government relations (the focus is on prestige), builds costly new facilities without apparent need and has an incomplete management team.

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[80] Woiceshyn, J. "Management — key to new product development in biotechnology." *Long Range Planning,* Vol. 26, No. 3, 1993, pp. 67-76.

Innovative logic is crucial to technology-based firms in their early stages of development since innovation and new product development truly are their life lines. The study concludes:

> An innovative logic can be cultivated by having an inventor–entrepreneur to lead the company. An inventor–entrepreneur would be someone with a strong desire to commercialize inventions and a significant ownership stake in the company. His [/her] scientific knowledge and ownership in the company would give him[/her] the power base to make the innovative logic dominant. Continuous, stable leadership in the early stages of the company's development, combined with a functionally complete management team, would also help to maintain the innovative logic.
>
> The innovative logic would in turn facilitate certain strategies and management processes leading to effectiveness in product development. First, the findings suggest that in order for NBFs to be effective, they need to consciously manage the broad external context including universities and government and to avoid dependence on the latter. In particular, collaboration with universities tends to accelerate their product development process. Second, building solid core competences as the basis of their market focus and aiming at either large target markets or markets without strong competition seem to pay off in effectiveness of product development. Third, management processes concentrating on acquiring and conserving resources, particularly long-term financing, and on R&D seem to facilitate effectiveness as well.[81]

In the pursuit of strategic alliances with multinational pharmaceutical companies to further their new product development, Canadian health care NBFs will typically undergo a rigorous assessment of the "value" of their business following the establishment of confidentiality agreements to protect their proprietary technologies. This evaluation usually focuses on most, if not all, of the elements sketched out in the aforementioned strategic model. For example, the multinational will send in a team with scientific, marketing and financial expertise to perform a technology assessment to determine the probable worth of the NBF's technology. The management type, structure and logics of action also undergo rigorous evaluation. As a consequence, it becomes possible to determine the probable cost and benefit of a potential strategic alliance as a basis for either striking a deal or walking away from the proposed alliance. This approach is being adopted increasingly by venture capital firms in the Canadian biotechnology community (viz., MDS Health Ventures).

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[81] Woiceshyn, J. "Management — key to new product development in biotechnology." *Long Range Planning,* Vol. 26, No. 3, 1993, pp. 67-76.

Other publicly traded Canadian NBFs circumvent the need (at least in the short run) to form strategic alliances by employing creative financing arrangements involving, for example, the floating of novel arrangements of stocks and warrants on public markets. However, as the Canadian investment community (including public and private markets serviced by brokerage houses, venture capital and merchant banking firms) develop more sophistication in their risk–benefit evaluations by turning to technology assessment expertise, the ability of fledgling NBFs to avoid this degree of scrutiny for their new product development will disappear rapidly.

To strengthen Canadian investor confidence in the Canadian biotechnology industry, it will be essential to deploy multidimensional approaches to technology assessment to assess the value of NBFs seeking infusions of capital. There are a significant number of early-stage firms who have never undertaken this integrated review of their business. For instance, some NBFs either lack appropriate intellectual property protection or have poorly characterized technologies. In such instances, no multinational would be willing to enter into a strategic alliance. The failure of these companies will erode investor confidence in this still nascent industry.

Strategic alliances (SAs) have been defined as collaborations between NBFs and other organizations, both short and long term, which can involve either partial or contractual ownership and are developed for strategic reasons. A recent study using data from interviews with 42 senior executives of NBFs in North America showed that the development and implementation of SAs can be broken down into three stages:

- the pre-alliance stage of matching suitable partners and negotiating the agreement between them;

- the alliance agreement stage in which the scope of the agreement, the resources to be allocated by partners and the definition of duties are set out; and

- the alliance implementation stage when mechanisms of communication are put in place.

The study confirmed that, for success to occur, the initial step in alliance formation is the vital one. NBFs with high levels of strategic alliance success had gone through a thorough initial screening process, i.e., a technology assessment. Furthermore, successful negotiating and developing of the alliance agreement relies heavily on paying attention to detail.[82]

An empirical analysis of the strategies of 89 biotechnology companies in R&D, marketing and technology acquisition found that:

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[82] Forrest, J.E. "Managment aspects of strategic partnering." *Journal of General Management.* Vol. 17, Summer 1992, pp. 25-40.

- in R&D, firms followed either an incremental or radical strategy;
- in marketing, either a defender or innovator strategy; and
- in technology acquisition, either a licensing or innovator strategy.

A radical R&D approach was linked with innovative technology acquisition and with a conservative marketing strategy.[83]

[83] Chakrabarti, A.K. "An empirical analysis of innovation strategies of biotechnology firms in the U.S." *Journal of Engineering & Technology Management*, Vol. 8, December 1991, pp. 243-260.

CHAPTER 3

BIOTECHNOLOGY TRENDS AND FORECASTS

3.1 Historical Trends

This section chronicles historical developments and scientific milestones to identify trends in the rate and significance of biotechnology innovation over the last 20 years. For projection purposes, it also attempts to identify the likely rate of innovation for projection purposes.

Although the term "biotechnology" has only been in common parlance for a couple of decades, its proponents have laid claim to human interventions involving biological processes stretching back to the earliest agricultural settlements. However, the field of biotechnology received its impetus from the 1953 discovery by Watson and Crick of the structure of the molecule bearing genetic information — deoxyribonucleic acid (DNA) — and it is only in the last two decades that the field of molecular genetics or recombinant DNA (rDNA) has evolved, with the ability to cut DNA into segments and then recombine DNA sequences from different organisms and transfer them to living cells. Current references to biotechnology include but are not confined to:

- cell fusion;
- rDNA technology;
- use of eggs and embryos;
- cell culture;
- tissue culture;
- advanced uses of microorganisms and enzymes;
- protein engineering;
- utilization of biomembranes and antibodies; and
- bioprocess engineering.

Although DNA's basic structure and means of replication were reasonably well deciphered by the late 1960s, manipulation of genetic sequences to alter an organism's genetic code was not demonstrated until 1973. At that time, two Americans, Boyer and Cohen, demonstrated a technique for splicing a gene from one organism into the genetic structure of another. In doing so, the second organism expressed proteins characteristic of the first. Scientific concern about the implications of this new technology led, in 1975 at the Asilomar Conference, to a voluntary moratorium on further research by most top American molecular biologists. Although the moratorium was never formally rescinded, the granting by the U.S. Patent Office of patent rights to the University of California for the Boyer and Cohen gene transfer technology in 1976 signalled a growing understanding and acceptance of discoveries in this emerging field.

On the research front, Milstein and Kohler of the British Medical Research Council Laboratory of Molecular Biology, in 1975, successfully fused cells from a mouse myeloma with cells derived from mouse B-lymphocytes to create a hybridoma, a self-replicating antibody-producing line of cells grown in-vitro. This research program (coupled with that of Boyer and Cohen) proved the feasibility of rDNA and monoclonal antibody (MAb) technology.[84] The first MAb kits were approved for use in 1981.

The Boyer and Cohen patent triggered commercial interest in recombinant technologies. In that year, Genentech Corporation became the first biotechnology firm launched in the United States to exploit rDNA technology. Within two years, Genentech had developed human insulin using this technology and, in 1982, this product became the first rDNA pharmaceutical to be marketed in both the United States and the United Kingdom. By 1979, Genentech had produced human growth hormone using rDNA technology and, in 1985, received Federal Drug Administration (FDA) approval to market the product. Genentech's initial public offering, in 1980, set a Wall Street record for the fastest rise in share price going from $35 to $89 in 20 minutes. In 1981, another U.S. new biotechnology firm (NBF), Cetus, set another Wall Street record by raising the largest ever amount of money ($115 million) through its initial public offering. By the end of that year, there were over 80 U.S. NBFs.

3.1.1 Canadian NBFs

In 1981, two Canadian NBFs were founded: Allelix Inc. (through a $60-million joint venture between the Canadian Development Corp., John Labatt Ltd and the Ontario government); and Quadra Logic Technologies (QLT).

Other Canadian companies quickly followed: Cangene in 1984, Hemosol Inc. and Biomira Inc. in 1985 (the latter with $9 million from Altamira Capital Corp.), Inutec Corp. (originally RML Medical Laboratories) and BioChem Pharma (originally IAF BioChem) in 1986 and the Biotechnology Research Institute and Plant Biotechnology Institute in 1987.

In 1988, Boehringer Ingelheim acquired Bio-Mega Inc. In 1989, Institut Mérieux of France purchased Connaught Biosciences Inc., and Ag West Biotech Inc. was founded. In 1991, Allelix and Cangene filed initial public offerings and were listed on the Toronto Stock Exchange (TSE). In 1993, Hemosol filed its initial public offering on the TSE and raised $35 million. By the end of 1993, Canadian publicly traded NBFs had achieved a market capitalization of $2.7 billion.[85]

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[84] Table extracted from *Biotechnology in a Global Economy*. U.S. Congress, Office of Technology Assessment, Washington, DC: U.S. Government Printing Office, October 1991, p. 4. (Additions have been included to expand the information.); Cohen, S., A. Chung et al. "Construction of biologically functional bacterial plasmids in vitro." *Proceedings of the National Academy of Sciences*, Vol. 70, 1973, pp. 3240-3244; Kohler, G. and C. Milstein. "Continuous cultures of fused cells secreting antibody of predefined specificity." *Nature*, Vol. 256, 1975, pp. 495-497.

[85] Going, T. and P. Winter. *Canadian biotech'94: capitalizing on potential.* Ernst & Young's third report on the Canadian biotechnology industry, Ernst and Young, 1994.

3.1.2 Capitalization and Profitability

In 1983, NBFs raised a total of $500 million in U.S. public markets. However, on Black Monday (October 19, 1987), the Dow Jones index fell 508 points and signalled a drying up of initial public offerings for NBFs in the United States and Canada over the next two years. NBFs turned to strategic alliances for investment and other support. In 1989, Gen-Probe became the first U.S. NBF to be purchased by a Japanese company. In 1990, Hoffman-LaRoche, a Swiss-based multinational pharmaceutical company, announced its intention to purchase a majority interest in Genentech. In 1991, U.S. NBFs sold $17.7 billion in new stock, the highest five-month total in history. In the same year, Chiron Corp. acquired Cetus Corp. for $660 million in the largest merger yet between two U.S. biotechnology companies.

By 1993 however, continuing depression in U.S. and Canadian biotechnology stock prices and demand resulted in a sharp increase in reported alliances between U.S. biotechnology firms and multinational drug manufacturers.[86] For example, in 1993, Rhone-Poulenc Rorer Inc. acquired a 37 percent stake in Applied Sciences Inc., a biological research firm specializing in the immune system, for $113 million and the right to increase its ownership stake to 60 percent by 1997. One report noted that buying shares in development-stage NBFs was very risky because they tended to go public so early in their life cycles that they were nearly as speculative as venture capital deals.[87]

Out of some 235 publicly traded U.S. NBFs in 1993, only six were profitable (only three were profitable in 1992: Amgen, Biogen and Genentech).[88] After many years of trying to get a proprietary product on the market, Genetics Institute, in collaboration with Baxter Healthcare, received FDA approval in 1993 for Factor VIII, the blood-clotting factor lacking in hemophiliacs. In late 1992, Cytogen received FDA approval to market the first MAb-based cancer imaging agent to be sold in the United States.

3.1.3 Government Support for Biotechnology

In the policy domain, the U.S. Supreme Court issued in 1980 a landmark ruling in *Diamond vs. Chakrabarty* that microorganisms could be patented. In 1987, the U.S. Patent and Trademark Office announced that non-human animals could be patented. Although the first transgenic animal had been created in 1973 and Palmiter et al. reported dramatic results in

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86 Rotman, D. "Biotech deal making soars, stock flop." *Chemical Week*, Vol. 153, August 18, 1993, p. 33.

87 Thayer, A.M. "Bottom fishing among the biowrecks: there may be bargains in this year's disaster sector." *Chemical & Engineering News*, Vol. 70, November 23, 1992, pp. 11-12.

88 Sheeline, B. "Health stocks that could gain 50% to 144%." *Money*, Vol. 22, May 1993, pp. 79-82.

experiments creating transgenic mice in 1982,[89] the first U.S. patent on an animal was not issued until 1988 for a transgenic mouse (the Harvard oncomouse) which had been produced using rDNA technology to contain cancer genes. The corresponding patent was issued by the European Patent Office in 1991.

Government support for biotechnology proceeded alongside these other developments. In 1980, both the United Kingdom (the Spinks Report) and the Federal Republic of Germany targeted government support for R&D in biotechnology. Japan followed in 1981 with the Ministry of International Trade and Industry (MITI) leading the way. In 1983, the Canadian government adopted the National Biotechnology Strategy (NBS) to fund biotechnology development in priority areas, particularly natural resource sectors of the economy (see Section 1.2). The U.S. government established its Co-ordinated Framework for the Regulation of Biotechnology published by the Office of Science and Technology Policy in 1986. In the same year, the U.S. *Technology Transfer Act* was passed providing expanded rights for companies to commercialize government-sponsored research. In 1988, the U.S. National Institutes of Health (NIH) launched an international collaborative program (which Canada joined in 1992 with $22 million in funding) to map the human genome.

3.1.4 Emergence of Second Generation Biotechnology Products

A growing list of health care biotechnology products and discoveries began to emerge during the 1980s. This included:

- the first automated gene synthesizer marketed in 1981;
- the first rDNA animal vaccine (for colibacillosis) approved for use in Europe in 1982;
- alpha interferon, the third rDNA therapeutic drug, approved by the FDA for the treatment of certain cancers in 1986;
- the cystic fibrosis gene identified by Dr. Lap-Chee Tsui of Toronto's Hospital for Sick Children in 1989;
- the first approval for a human gene therapy clinical trial in the United States in 1990; and
- the gene for Huntington's Chorea identified in 1993.

Some of the more important biotechnology drugs and products which have been approved for human use include:

- Factor VIII, a replacement molecule for patients with hemophilia A;
- Glucocerbrosidase, an enzyme replacement for victims of Gaucher's Disease;
- interleukin-2 for use in cancer treatment;

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[89] Palmiter, R.D., R.L. Brinster et al. "Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes." *Nature*, Vol. 300, 1982, pp. 611-615.

- tissue-plasminogen activator (tPA), a clot-dissolving agent used in heart attacks;
- Erythropoietin (EPO) for the treatment of anemia associated with chronic renal failure;
- hepatitis B vaccine; and
- growth colony-stimulating factor used as an adjunctive to chemotherapy.

There are currently about 20 new proteins, interferons, colony-stimulating factors, thrombolytic enzymes and peptide hormones registered as drugs, some with outstanding therapeutic prominence.[90] The 1993 Pharmaceutical Manufacturers' Association (PMA) survey reported 143 biotechnology products under development or waiting for FDA approval. These products involved 63 companies and 170 separate projects (since some products are under examination for more than one indication).[91]

Biopharmaceuticals have touched and improved every branch of medicine, bettering the prospects for patients with hairy cell leukemia and other forms of cancer, heart disease and genetic diseases. Many biopharmaceuticals have proved cost effective in the current climate of health care cost containment.

An accelerating pace of discovery has affirmed biotechnology's scientific potential and scope. However, the industry's financial viability continues to face challenges. Investors worry that drug cost controls will limit the return on even the very best biopharmaceutical products. To ensure continued development in biotechnology, inventors of successful products will need to be rewarded sufficiently to provide the incentives to continue discovering new therapies.

By the year 2000, biotechnologists' armamentaria will comprise trillions of compounds generated by random libraries and evolutionary biology. Combine these resources with a growing understanding of the genome as a whole and the burgeoning ability to construct molecules by computer, and the medicine of the 21st century will bear little resemblance to current practice.[92]

In agricultural biotechnology, 1983 saw the first expression of a plant gene in a plant of a different species. By 1990, the FDA had approved recombinant rennin, an enzyme used to produce cheese which became the first bioengineered food additive to be approved in the United States. It was approved for sale in Canada shortly afterward. In the same year, Micogen became the first company to begin large-scale testing of a genetically engineered

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[90] Drews, J. "Into the 21st Century: Biotechnology and the pharmaceutical industry in the next ten years." *Bio/Technology*, Vol. 11, 1993, pp. S16-S20.

[91] "PMA survey shows 143 biotech medicines in development." *Medical Marketing & Media*, Vol. 28, November 1993, p. 62.

[92] Bud, R. "100 years of biotechnology." *Bio/Technology*, Vol. 11, March 1993, pp. S14-S15; Rathman, G.B. "Knocking on opportunity's window." *Bio/Technology*, Vol. 11, March 1993, pp. S27-S32.

biopesticide. In 1991, the U.S. Environmental Protection Agency (EPA) approved the first genetically engineered biopesticide for sale in the United States. In 1994, the Flavr-Savr tomato (engineered for long shelf life) and bovine somatotropin (rbST) (a recombinant product which increases milk production in dairy cows) were approved by the FDA for sale in the United States.

In environmental biotechnology, a U.S. NBF, Advanced Genetic Sciences, Inc., received the first experimental-use permit ever issued by the EPA for small-scale environmental release of an rDNA organism in 1985. The 1989 *Exxon Valdez* oil spill attracted world attention to the use, for bioremediation purposes, of microbe-enhanced fertilizers — biofertilizers.

3.1.5 The Rate of Biotechnology Innovation

One means employed by economists to estimate the "rate of innovation" is to track publication rates. One study used the on-line biomedical data base EMBASE to determine the proportion of biomedical papers originating from U.S. and Japanese institutions appearing in 49 U.S. and 63 English-language, European journals. The proportion of U.S.-authored papers in U.S. journals declined from 80 percent in 1978 to 65 percent in 1990. In European journals the proportion remained steady at 20 percent to 25 percent. Over this period, the contributions from Japanese authors in both American and European journals increased from 2 percent to 6 percent.

While some have suggested that the decrease in the number of U.S.-authored biomedical papers is linked to slowed growth in funding from the National Institutes of Health, the study suggests it may have more to do with the high standards of non-U.S.-authored publications.[93]

There is support in the literature, therefore, for the view that the rate of innovation during the 1978 to 1990 period remained relatively constant. However, U.S. (and Canadian) market pessimism, beginning in 1992, led to a decline of 6 percent in the market capitalization of the U.S. biotechnology industry from 1993 to 1994[94] which suggests a decline in the rate of growth in innovation as a result of a decline in the confidence of short-term U.S. investors.

The continuing commitment to biotechnology by the U.S. and Canadian governments can be expected to sustain R&D activity, the longer-term investment climate and the rate of innovation in both countries. This prognosis would have to be modified if the Canadian government resorted to short-term fiscal expediency measures at the expense of the

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[93] Sodha, R.J. "Trends in biomedical publications: US and Japanese authors in US journals and European journals." *Journal of Information Science Principles & Practice*, Vol. 19, 1993, pp. 71-73.

[94] University of Toronto Innovations Foundation. "Innovations Foundation licenses technology to Canadian Pork Council." IF News Release, Toronto, Canada, February 22, 1993; Soto, S. "Pig patent proves profitable." *University of Toronto Bulletin*, April 12, 1993; "Cotswold launch halothane-free high-lean boar." *Cotswold NOW!*, Spring 1993.

country's fledgling biotechnology community.

3.2 State of the Art Technology

This section provides an overview and understanding of the current science, state-of-the-art technology and commercial uses of biotechnology specifically focusing on the most important sectors of the economy using lifeforms, and on microorganisms and products of organisms.

3.2.1 Biopharmaceuticals[95]

The Cohen–Boyer gene splicing experiment in 1973 showed how it was possible, using rDNA techniques (i.e., enzyme-based methods for manipulating pieces of DNA), to slice a gene out of the genome of a mammal and insert it into a microorganism. The implications were enormous. On the one hand, animal genes could be cloned and studied in unprecedented detail. On the other, a scientist could genetically "program" bacteria to produce proteins. Elusive, fragile proteins which had hitherto been impossible to isolate, let alone use as drugs, soon became available as rDNA proteins to treat a host of human diseases. In the following years, powerful new techniques were added to the rDNA tool box. The polymerase chain reaction (PCR) has allowed researchers to amplify tiny scraps of DNA, while the development of better methods of inserting DNA into host genomes promises a new era of transgenic plants and animals (e.g., maize with genes to ward off pests, tomatoes with genes to keep them fresh or mice carrying human genes).

Worldwide, about two thirds of all biotechnology companies are focused on therapeutic or diagnostic applications. In Canada, the figure is about 64 percent. Worldwide, about 10 percent of biotechnology companies are applying biotechnology to food and agriculture. In Canada, the figure is about 23 percent. Applications in the chemical industry and to clean up the environment account jointly for just 8 percent of worldwide activity but 12 percent of activity in Canada. The remainder of the firms either license out or supply services and instrumentation to other biotechnology, chemical and pharmaceutical firms. The emphasis on health care is due to the presence of a profitable marketplace, while investors are less sure about prospects for biotechnology in food processing and environmental protection.

Therapeutic proteins continue to be the biggest money spinners for the biotechnology industry. Some 20 recombinant proteins, ranging from blood clotting enzymes and hormones to interferon proteins that stimulate immune cells, are now on sale as drugs, and seven times that number are in clinical development. It has been estimated that an average of at least five new proteins will become available each year and, over the next five years, rDNA proteins will account for at least 10 percent of all profits from new drugs, bringing

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[95] Coghlan, A. "Engineering the therapies of tomorrow." *New Scientist,* Vol. 138, No. 1870, April 24, 1993, pp. 26-31.

in revenues of between $10 billion and $20 billion in the United States.

However, the road has not been smooth or untroubled. Over the last five years, many companies have floundered, flagship proteins have flopped in clinical trials and courtroom patent battles have gobbled up time and money. These events are also helping to shape the future of biotechnology.

The biggest problem facing biotechnology companies developing therapeutic proteins today is the vast amount of money and time ($230 million and 12 years per protein, according to the U.S. Pharmaceutical Manufacturers' Association) required to put these products through rigorous clinical trials. In addition, these companies have little experience in dealing with stringent regulatory bodies [viz., the U.S. FDA and Canada's Health Protection Branch (HPB)].

One such example is tissue plasminogen activator (tPA), a therapeutic enzyme from Genentech which has been sold under the trademark Activase since 1987. It dissolves blood clots and can help open blocked arteries in heart attack victims. Sales plummeted in 1991 when clinical results suggested that tPA was no more effective in saving lives than a conventional and much cheaper drug, streptokinase. A more recent study provides statistically significant evidence of the drug's efficacy although the results have been questioned because of their lack of clinical significance (by increasing the survival rate for heart attack victims by about 1 percent, they imply a cost effectiveness of about $100,000 per saved life).

Other flagship proteins fared much worse. In 1989, an rDNA protein emerged from Genentech known as "soluble CD4"which could stop HIV from infecting cells in in-vitro studies. The protein was a soluble form of the receptor molecule which HIV subverts in order to invade cells, and the aim was for the protein to act as a molecular decoy, sticking to virus particles and preventing them from infecting cells. Four years later, having spent millions of dollars testing soluble CD4 in patients with HIV, Genentech all but abandoned the project. The clinical trials were disappointing because of basic science problems affecting this field of biotechnology application. Proteins are digested by stomach enzymes before they have a chance to reach the bloodstream. As a result, proteins have had to be delivered as injectables. However, injected proteins also enjoy only a fleeting existence in the bloodstream before being broken down by enzymes. And it is virtually impossible for proteins to pass across cell membranes. Soluble CD4 was no exception, and its early promise was not sustained clinically.

Other more spectacular setbacks have included a monoclonal antibody known as HA-1A, or centoxin (by Philadelphia-based Centocor) and another drug, Antril. Centocor began developing the antibody in the mid-1980s as a treatment for septic shock, a blood-poisoning condition caused by bacterial infections. Lab tests suggested that the antibody might "neutralize" the bacterial substance thought to trigger septic shock. The first clinical trial seemed to support this hypothesis. Further trials cast doubt on the antibody's efficacy, and it was withdrawn from studies by Centocor in 1993. Similarly, Antril, another drug for septic shock, was withdrawn, also in 1993, after clinical trials showed it to perform little

better than a placebo.

These failures have chilled financial markets, and have caused biotechnology companies to seek financial support from traditional pharmaceutical companies. Persuaded by the big profits of early entrants into biotechnology, major drug companies starting with Hoffman-LaRoche, which bought 60 percent of Genentech for $2.2 billion in 1989, began to form strategic alliances, joint ventures and other relationships with biotechnology firms and institutes. Sandoz signed a deal with Systemix, Cyanamid with Immunex and American Home Products with the Boston-based Genetics Institute. In Canada, Glaxo entered into an agreement with Allelix Biopharmaceuticals.

These alliances not only provide new sources of funding for biotechnology, they facilitate product and technology transfer through licensing agreements which enable biotechnology firms to diversify and reduce the uncertainties in their product development. They also reflect a more mature understanding on the part of the larger pharmaceutical firms that they cannot afford to do research in all therapeutic categories in the face of exponential growth in knowledge in the biological sciences and the burgeoning of cutting-edge technologies.

Instead of concentrating on producing rDNA proteins which have been the mainstay of biotechnology since the early 1970s, the next generation of researchers are exploiting a much broader range of routes to drugs. There are some 200 biotechnology companies in the United States (e.g.,Genzyme, Tularik, Cell Genesys and Gilead) and others in Canada and elsewhere which are pursuing newer technologies such as small molecules and rational drug design as therapeutic alternatives. It has become clear that DNA, ribonucleic acid (RNA), a protein or a carbohydrate, or some other small molecule can be used to treat patients. The research focus has switched to developing an understanding of disease mechanisms.

For instance, Tularik scientists are concentrating on finding small molecules to treat viral diseases and to clear cholesterol from the blood. In both cases, they are looking for clues in the behaviour of transcription factors — proteins that act as molecular switches inside cells, turning genes on and off.

Transcription factors are vital to viral replication. Once inside the cells, viruses insert their genes into the host's chromosomes. At a later stage, they "subvert" one or other of the host's transcription factors to activate these genes. Tularik's aim is to identify the transcription factors used by particular viruses, such as Vp16 in the herpes simplex virus, and then screen for compounds that will block their action. Rather than using rDNA technology to make proteins, the search is on for methods to alter disease mechanisms.

Tularik hopes to approach the problem of cholesterol in a similar manner. This time though, its researchers are looking for compounds that mimic, as opposed to block, transcription factors. They will be targeting transcription factors that stimulate cells to produce certain receptor molecules — compounds that mop up cholesterol in the bloodstream.

Cell Genesys (Foster City, California) is exploiting homologous recombination — a way of inserting DNA, at will, anywhere along a chromosome. The technology is intended to interfere with gene expression, so genes can be silenced or switched on by the inserted material. Through greater knowledge of the structure and location of genes in the chromosome, the application of gene targeting is widening. This technology has enabled the development of specialized T cells — components of the body's immune system — to destroy cells infected with HIV. Normally, T cells will only work in the individual from whom they came. In anyone else, they are "blind" to the things they were meant to attack. The company's scientists have found a way to "silence" the gene which makes human leukocyte antigens — the proteins on the surface of T cells which stop the cells working in other people. They have also equipped the T cells with means to "recognize" cells infected with HIV.

A host of other technologies on the horizon threaten to make proteins redundant. One is the so-called antisense approach to silencing genes which, at least in cells in-vitro, can be used to stifle the production of problematic proteins such as those involved in viral replication. The basic idea behind antisense is that the production of an unwanted protein is sabotaged with a sequence of RNA which binds to, and neutralizes, the gene which carries the instructions for making the protein or to the messenger RNA which actually makes the protein.

Gilead (Foster City, California) is using small nucleotide sequences designed to "fill" the gullies in a gene's double helix so it forms an inactive triple helix. One of the company's most closely guarded secrets is the chemical trickery it uses to modify nucleotides so they are able to sneak into cells through the cell wall. Another company, Isis Pharmaceuticals (Carlsbad, California), is evaluating an antisense gel for genital warts. An antisense gel has already worked in rats to prevent blocked arteries.

Another post-protein technology creating excitement is gene therapy. Scores of technical problems remain, but it is less than three years since the ground-breaking experiment at the National Institutes of Health in Bethesda, Maryland. Defective white blood cells were taken from a young girl with adenosine deaminase deficiency (an inherited condition in which people have a weakened immune system), corrected genetically and replaced. Trials are now well advanced to evaluate the effectiveness of this and other gene therapies.

While some 100 gene therapy procedures have been approved and are in clinical trials in the United States and Europe, which gene therapy companies will be the winners in the marketplace? The promise of gene therapy is being pursued by dozens of companies, several of which are public or have been acquired by large biotech companies. Cell Genesys does gene targeting and Genetic Therapy specializes in a mouse-derived retrovirus. SyStemix is in a joint venture with Switzerland's Sandoz that is focusing on gene therapy to develop HIV-resistant cells. A number of companies produce hardware and supplies used in the production of gene therapies. One is Applied Immune Sciences, 37 percent owned by Rhone-Poulenc Rorer. Two such U.S. NBFs, Transkaryotic Therapies and Viagene,

failed in their initial public offerings (IPOs) last year.[96]

Genetic Therapy (Gaithersburg, Maryland) is developing gene therapies for lung cancer, breast cancer, cystic fibrosis and Gaucher's Disease. In one company trial, six people received a form of gene therapy to combat brain cancer. Other companies (Viagene and Somatix in California, and Genzyme in Boston) are seeking approval for clinical trials with gene therapy.

In Britain, the Medical Research Council has recently set up a company, Therexsys, to commercialize gene therapy technologies developed by its researchers. Treatments for cystic fibrosis are also proceeding. According to one estimate, if gene therapy proves successful, it could eventually replace about $12 billion in drug sales.

A renaissance is already under way in one of the oldest technologies in the drug industry: natural product screening. Once shunned as old hat by molecular biologists, screening is fast becoming a key activity in biotechnology companies. Xenova, a British company based in Slough, Berkshire, specializes in trawling through natural products for possible drug leads, and has forged strong links with biotechnology firms such as Genentech. It claims to have the largest library of fungi in the world, with 23,000 varieties. Fungi are considered a rich source of candidate drugs.

But possibly the most advanced approach to screening yet devised is at Affymax (Palo Alto, California). Beginning with the idea that one can accelerate drug discovery by evaluating hundreds of thousands of compounds at once, the company has assembled scientists with training in disciplines ranging from semiconductor technology and software development to chemical synthesis and biology. The aim is to screen and synthesize in parallel, and the result has been screening on a microchip. The company can synthesize and screen 65,000 compounds in 48 hours on a one-centimetre-square chip. With the help of precise computer-controlled machinery that manoeuvres a masking plate above the chip, and light-sensitive chemicals, engineers are able to lay down grids of nucleotides layer by layer. It has become possible to make all 65,536 (2^{16}) sequences that are possible with eight nucleotides in just 32 steps on a four-by-four grid, according to Affymax's scientific director.

In the final screening step, the chip is exposed to the "target" molecule against which activity is sought, and a special light-sensitive tag on the target shows which drug candidates have bound most strongly when the chip is illuminated with a laser. The technology, called very large scale immobilized polymer synthesis, is ideally suited to storing and accessing data from the human genome project, and Affymax was recently awarded $2.2 million from the National Institutes of Health for that purpose. For example, the 200 or so genetic mutations that cause cystic fibrosis could be incorporated into a single chip which would indicate immediately from a sample of DNA whether one of the mutations was there. Affymax could be the first of a new generation of companies which combines gene technology with computer technology, sometimes called nanotechnology.

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96 Mortenthaler, L. "Just what the doctor ordered." *Barron's*, Vol. 73, September 20, 1993, pp. 10-11.

In summary, biotechnologists hope to develop drugs which can halt disease by blocking troublesome genes (code blockers, triple helix) or their RNA messages (code blockers, antisense) as well as problematic proteins within the cell (using small molecules) or outside the cell (using aptamers — small artificial DNA molecules).

3.2.2 Agricultural Biotechnology (AgBio)[97]

Agbio research can be grouped into six categories.

1. **Gene identification** locates and identifies agriculturally important genes and creates chromosome maps.

2. **Gene regulation** understands the mechanisms of regulation and expression of these genes and refines the methods by which they may be genetically engineered.

3. **The structure and function of gene products** need to be understood in metabolism and for the development of agriculturally important traits.

4. **Cellular techniques** are used to develop and refine techniques for cell culture, cell fusion, regeneration of plants and other manipulations of plant and animal cells and embryos.

5. **Development in organisms and communities** leads to understanding the complex physiological and genetic interactions and associations that occur within an organism and between organisms.

6. **Environmental considerations** refer to understanding the behaviour and effect of rDNA organisms in the environment.

Throughout the history of agriculture, humans have taken advantage of the natural process of genetic exchange through breeding that creates variation in biological traits. This fact underlies all attempts to improve agricultural species, whether through traditional breeding or through techniques of molecular biology. In both cases, people manipulate a natural process to produce varieties of organisms that display desired characteristics or traits such as disease-resistant crops or food animals with a higher proportion of muscle to fat.

The major differences between traditional breeding and molecular biological methods of gene transfer lie in speed, precision, reliability and scope, not in goals or processes. When traditional breeders cross two sexually reproducing plants or animals, thousands of genes

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[97] Hess, C.E. (Chairman). *Agricultural Biotechnology: Strategies for national competitiveness.* Washington, DC: National Academy Press, 1987.

are mixed. Each parent, through the fusion of sperm and egg, contributes half of its genome (an organism's entire repertoire of genes) to the offspring, but the composition of that half varies in each parental sex cell and hence in each cross. Many crosses are necessary before the "right" recombination of genes result in offspring with the desired combination of traits.

Molecular biological methods alleviate some of these problems by allowing the process to be manipulated one gene at a time. Instead of depending on the recombination of large numbers of genes, scientists can insert individual genes for specific traits directly into an established genome. They can also control the way these genes express themselves in the new variety of plant or animal. In short, by focusing on a desired trait, molecular gene transfer can shorten the time required to develop new varieties and give greater precision. It can also be used to exchange genes between organisms that cannot be crossed sexually.

Gene transfer techniques are key to many applications of biotechnology. The essence of genetic engineering is the ability to identify a particular gene — isolate the gene, study its function and regulation, modify the gene and reintroduce it into its natural host or another organism. These techniques are tools, not ends in themselves. They can be used to understand the nature and function of genes, unlock secrets of disease resistance, regulate growth and development, or manipulate communication among cells and among organisms.

Monoclonal antibodies (MAbs) are the product of cell fusion technology and can be used to identify complex proteins and macromolecules. They are powerful tools in molecular analyses, and their uses in detecting low levels of disease agents, such as bacteria and viruses, are rapidly expanding.

Beyond many diagnostic uses, hybridoma technology shows promise for immunopurification of substances, imaging and therapy. Immunopurification is a powerful technique to separate large, complex molecules from a mixture of either unrelated or closely related molecules. For imaging, easily visualized tags can be attached to MAbs to provide images of organs and to locate tumors to which the antibody will specifically bind. Finally, new therapeutic methods have been developed that use MAbs to inactivate certain kinds of immunological cells and tumor cells or to prevent infection by certain microorganisms.

Many applications of MAb technology are finding their way onto the marketplace. The commercial agricultural use of MAbs now includes therapeutics against calf and pig enteric colibacillosis which causes neonatal diarrhea (scours). This approach is often more effective than conventional vaccines, and it supplements rDNA vaccines. MAb-based diagnostic kits can detect whether scouring animals are infected with a particular strain of bacterium that causes scours. This helps veterinarians determine the appropriate therapeutic MAb to use on an infected herd.

The productivity improvements in agricultural crop yields over the last 50 years have been made possible by advances in science and technology that have enabled more intensive use of yield-enhancing inputs such as fertilizers and pesticides. Yet these productivity successes brought about by farm mechanization, improved plant varieties and the development of

agricultural chemicals may be harder to repeat in the future unless new approaches are pursued. Biotechnology offers the potential to improve the efficiency of crop production by lowering the cost and increasing the quality of food. For instance, the tools of biotechnology can be harnessed to develop higher yielding and more nutritious crop varieties, to improve resistance to disease and adverse conditions, or to reduce the need for fertilizers and other expensive agricultural chemicals.

The efficiency of crop production can be enhanced through genetically engineering plants to create "transgenic" plants. Researchers can screen generations of plants for a specific trait or work more quickly and precisely to transfer a trait. The process is not simple. Typically, researchers must isolate the gene of interest, insert it into a plant cell, induce the transformed cell to grow into an entire plant and then make sure the gene is appropriately expressed.

Such transgenic plant successes have already happened. Herbicide-resistant traits are being transferred to crop plants to increase options for controlling weeds. In Canada, open field trials have begun to test certain transgenic varieties. As well, the composition of storage proteins, oils and starches in plants may be altered to increase their value.

Another success in this area is the extraction of a sulfur-rich protein gene from the Brazil nut (the gene expresses a protein containing large amounts of two nutritionally important sulphur-containing amino acids: methionine and cysteine). If this gene could be transferred to legumes deficient in these nutrients, such as soybeans, it would enhance the legume's role as a protein source throughout the world. The gene has been successfully isolated, extracted and transferred into tomato and tobacco plants, and into yeast cells. The technology is progressing toward the day when this enriched soybean may become a scientific and commercial reality.

Similar work is being done to improve oil crops. Depending on their chemical composition, oils and waxes from plants have uses in feed, food and industrial products such as paints and plastics. Through knowledge of the enzymes controlling the biochemical pathways that regulate molecular chain length, degree of saturation and, hence, the chemical properties and uses of plant oils, scientists are deploying genetic engineering to modify oil composition of some crops.

Scientists are now studying the potential of engineering plants to take advantage of the properties of specific plant species. For instance, crabgrass naturally produces a chemical (called an alleopath) to prevent other grasses from invading its territory. By engineering a crop plant with a similar trait could it control weeds in the same way? The task is difficult, in part because of the difficulty in understanding how certain plants produce alleopathic molecules and at the same time protect themselves against these chemicals.

Agricultural scientists have determined that plant growth and developmental processes are influenced by a relatively few plant hormones or growth-regulating substances. A number of plant inhibitors and mimics of these regulating compounds have been discovered and have readily found commercial applications. For example, they are used to induce and

synchronize flowering and fruit production in pineapple fields, to control ripening and premature dropping of fruit from trees and vines, and to block elongation growth to create more compact and attractive potted plants, such as chrysanthemums and poinsettias.

Gene probes and related technologies have increased knowledge of the natural growth regulators of plants. As a result, scientists can improve on ways to control fruit ripening, so ripening can be delayed until the fruit is en route to market (i.e., improving the "shelf life" of edible fruits and vegetables). Scientists are developing ways to increase flowering, fruiting, seed set and other growth habits of plants to improve efficiency of production.

Microorganisms in the environment affect the growth of plants in a variety of ways, many of which are still poorly understood. Their effects can be either beneficial or harmful. For instance, some microorganisms protect plants from environmental stresses such as acidity, salinity or high concentrations of toxic metals. Still others attack weeds that compete with crops. The best known association between microorganisms and plants is the symbiotic relationship between certain nitrogen-fixing bacteria and members of the legume family such as soybeans.

However, some microorganisms, particularly certain bacteria and fungi, are pathogens that attack crops and cause disease, sometimes in epidemic proportions. The Irish potato famine of the mid-1800s, the Dutch elm disease of the 20th century and the southern crop leaf blight of 1970 are dramatic examples of losses caused by pathogens.

As our understanding of the relationships between microorganisms and crops improves, the genes controlling these relationships — whether in the microorganism or in the plant — can be engineered to enhance the abilities of beneficial microorganisms or inhibit the effects of harmful microorganisms. Yet to engineer microorganisms successfully, scientists must understand the molecular mechanisms by which they interact with their plant hosts. Much remains to be learned about both the plant and the microbial genes involved, their regulation and the intricate relationships between microorganisms and their hosts.

Initial discoveries in rDNA technologies were made with microorganisms because they are simpler lifeforms than higher plants and animals, and are easier to manipulate in the laboratory. Methods developed in medical research with bacteria and viruses are now being adapted to agriculturally significant microorganisms. One example involves genetically altered bacteria designed to prevent frost damage. *Pseudomonas syringae* is a bacterial species with many members that are normally harmless and commonly inhabit the outer surface of plant cells. However, some of these bacteria contain a protein that initiates the formation of ice crystals at temperatures below freezing. The growing ice crystals can rupture and damage plant cells. If the bacteria are not present, plants can withstand colder temperatures without damage. Researchers have now created an "ice-minus" strain of the bacteria by removing the gene that makes the protein. In laboratory tests the ice-minus strain has been sprayed on plants to displace the wild strain and provide the crop with some measure of frost protection. Field tests to test its commercial application were blocked by public apprehension and court actions.

Another practical application involves the use of DNA probes to detect plant viruses and viroids. Detection permits rapid screening to eliminate infected stock and halt the spread of diseases.

Nearly 60 years ago, scientists found that a mild strain of tobacco mosaic virus (TMV) could protect tobacco plants against the adverse effects of a subsequently inoculated, severe strain of the virus. This phenomenon, termed "cross-protection," has been applied on a limited scale to protect greenhouse tomatoes and a few orchard crops. There are potential problems with the conventional cross-protection approach, because the mild, protecting virus might spread to other crops or mutate to a more virulent form. Recently, scientists installed fragments of the TMV genome in tobacco and tomato plants. Because these transgenic plants have only a portion of the genetic information that is needed for TMV replication, the problems of conventional cross-protection are avoided. Some transgenic plants appeared to be completely resistant to the TMV virus. Tests show that virus resistance introduced by rDNA technology can be transmitted through seed as a simple Mendelian trait and can thus be transmitted by conventional breeding techniques.

Genetic engineering to improve nitrogen fixation is proving particularly challenging. All living things need nitrogen, yet plants cannot directly absorb and use nitrogen gas, which makes up more than 75 percent of the atmosphere. To be available to plants, nitrogen gas must first be "fixed," or converted into nitrogen-containing compounds either by industrial processes or by certain bacteria and blue-green algae that live in the soil. The best-known bacteria to fix nitrogen belong to the genus *Rhizobium*, which associates with members of the legume family such as soybeans, beans, peas, peanuts, alfalfa and clover. Genetic engineers would like to find ways to improve nitrogen fixation in these plants and extend the ability to others. This development could play a critical role in lowering production costs by reducing the need for energy (petrochemical) inputs used in producing nitrogen fertilizers. Another problem in this area occurs in the field: laboratory-modified rhizobial inoculants lose out to competing indigenous strains.

Another strategy to improve crop production through genetic engineering involves protecting crops from pests. Insects, viruses, bacteria, fungi, nematodes and weeds can impair agricultural productivity. Yet in a natural ecosystem, organisms typically serve many functions. Insects, for example, can be pests — destroying crops and stored products and transmitting disease. They can also be benefactors — pollinating plants, eating other pests and recycling organic wastes. Most chemical insecticides, herbicides and other pesticides that have been the primary methods of controlling pests are not selective enough to affect only harmful organisms. As biotechnology becomes more refined, methods for handling bothersome pests and beneficial organisms will be created. For example, the potential exists to identify the genes controlling certain plant properties that produce chemicals which mimic insect hormones and disrupt the reproduction of insects feeding on plants. Companies have identified a hormone which controls maturation in insects, and have created a juvenile hormone analogue in the form of a synthetic chemical compound. When sprayed on an insect, the insect remains in an immature state and dies instead of maturing and reproducing. A spray version is currently being marketed for flies, mosquitoes, fleas and cockroaches.

Another example involves genetically altering a bacterium — a strain of corn-root colonizing bacteria — to provide insecticide properties against black cutworm and other pests. The rDNA bacterium is freeze-dried and coated directly onto seeds before planting, or it can be sprayed onto fields directly. The product in question affects a small range of insects, and the company aims to have a prototype ready for the market in the 1990s. Another company is working to transfer the toxin gene into plants themselves to make them self-protecting against pests. Similar approaches are being used to find genes which control resistance or toxins against nematodes.

Recombinant DNA technology is being used to harness naturally occurring insect pathogens, including bacteria, viruses and fungi, as agents of biological pest control. Pathogenic viruses, such as baculoviruses, are considered promising. These viruses are inherently safer to work with than other insect viruses because they do not infect vertebrates or plants. Another speculative approach to control sucking insects would be to insert an insect-specific toxin gene or behaviour-modifying gene into the genome of the plant virus, so it is expressed in the cells of the insect. Various fungi, known to cause widespread diseases in insect populations, are being investigated as forms of pest control as well.

For centuries, people have sought to improve animal productivity by selecting and breeding only the best animals. Breeders have sought to develop animals that grow bigger, produce more, provide leaner and better-quality products, use resources more efficiently or show increased fecundity or resistance to disease and stress. Today, for instance, half the number of cows are producing the same amount of milk as did cows 30 years ago, while consuming one-third less feed. This is mainly the result of controlled breeding, coupled with improved feeding and other management practices.

Greater knowledge of reproductive biology and the genetic basis of traits has given breeders new tools to accomplish these goals. Artificial insemination has revolutionized animal breeding. Embryo transfer for livestock animals is another industry that has changed the nature of cattle breeding. The next advances will come from combining conventional breeding methods with new rDNA technologies. These new methods will give breeders unparalleled precision in manipulating desired traits while speeding up the process.

Currently, MAbs are being used as animal diagnostic aids (e.g., for diagnosing pregnancy in cows and for determining when dairy cows come into estrus to improve timing of artificial insemination and maintain maximum milk production). However, the technology of gene transfer in animals is still in its infancy. One complicating factor is that, unlike plants, animals cannot be regenerated asexually. A foreign gene can only be introduced into all the cells of an animal, including the cells that allow it to pass the trait to its offspring, by inserting the foreign DNA into germ cells, sperm or egg, or into the product of their union, the zygote. Another complicating factor is that many production traits (e.g., muscle growth, number of offspring and milk production) are controlled by many different genes.

Low-cost production of large quantities of animal growth hormones could improve production efficiency. An rDNA version of BST or bovine growth hormone (BGH), a naturally occurring hormone that increases milk production in cows, was recently approved

for marketing in the United States. It is claimed that the animal's milk composition does not change, although it does require greater amounts of and more nutritious feed. Recombinant porcine growth hormone (PGH) has also been developed to elevate pigs' growth rate, feed efficiency and ratio of muscle to fat but has yet to reach market. Attempts to transfer the growth hormone gene to laboratory mice have not been entirely successful.

In the area of fish farming, the science of aquaculture is relatively young. However, by manipulating fertilization to produce triploid and tetraploid fish, it is possible to produce sterile progeny, thus ensuring maximum growth because no energy is "wasted" on reproduction. Scientists can also regulate the sex of fish through treatments to produce more female fish which are preferred by commercial markets. Microinjection of growth hormones has proven effective in promoting fish growth, and rDNA manipulation is under way to augment fish growth hormones. To improve fish tolerance to cold temperatures, rDNA methods are being employed to transfer an "antifreeze" gene from winter flounder (and other Antarctic fish) to other fish species to enable them to live at colder temperatures, both for propagation in the wild and in aquaculture ponds.

Biotechnology is being used to diagnose, prevent and control livestock and poultry disease. MAbs hold great potential to diagnose disease, monitor the efficacy of drugs and develop therapeutic treatments and vaccines to immunize against certain diseases. MAb diagnostic tests and therapeutic treatments are available for calf and pig scours as described above. MAb diagnostic kits are also on the market for other diseases (e.g., bluetongue, equine infectious anemia and bovine leukosis virus). However, some farmers may not be able to afford to use these products which may be limited to high-value animals.

Biotechnology is being used to develop animal vaccines against viral diseases, which are generally resistant to antibiotic treatment. For example, rDNA preventive vaccines for foot-and-mouth disease are under development. Such vaccines are effective, safe, easy to manufacture, economical to produce, have long shelf lives, are stable at ambient temperatures and do not contain lethal infectious viruses (thus avoiding the potential problem of inadvertently causing the disease one is vaccinating against). Genes have been cloned for the surface proteins of viruses that cause fowl plague, influenza, vesicular stomatitis, herpes simplex, foot-and-mouth disease and rabies. And experiments are under way for other animal disease vaccines. Before their routine and widespread use, however, questions remain about vaccine side effects, dosages and timing of applications.

R&D of rDNA vaccines is time consuming, because each disease, and the many pathogenic strains causing it, must be investigated individually. For each disease, a specific immunogenic antigen must be identified, and the appropriate gene must be isolated and transferred into a bacterium or other fermentable organism, such as yeast, to allow its manufacture in large quantities. The first commercial application of an rDNA vaccine to immunize swine against pseudorabies, a serious livestock disease, has become available. The vaccine consists of pseudorabies viruses that are altered to prevent them from causing disease but are still capable of triggering the production of antibodies.

The world's first effective vaccine, a non-lethal virus called cowpox, was used in the 18th century to combat the lethal human disease smallpox. Modern scientists developed the related vaccinia virus to eliminate this scourge from the world. Vaccinia is a non-lethal, non-pathogenic virus that conveys a strong and lasting immunity, is easily and cheaply manufactured, can be transported without refrigeration or loss of potency, and can be injected under non-sterile conditions with a jet gun. For these and other reasons, an rDNA version of vaccinia would be an ideal candidate to combat other diseases, both of humans and of agriculturally important animals.

Vaccinia is basically a delivery system. Given appropriate protocols, any gene can be moved into vaccinia and be carried into the recipient of the vaccine. This means that the virus can be adapted to combat any selected disease. As a large, complex virus, a vaccinia virus could accommodate simultaneously at least a dozen foreign genes and still successfully immunize against a dozen different diseases. Research in this field is under way.

Research in the use of rDNA technology to alter the intestinal bacteria of ruminant farm animals to make them more efficient in using plant waste fibres is under way as well.

Age-old procedures (e.g., fermenting grape juice or leavening bread dough) are forms of bioprocessing. Bioprocessing also includes a range of technologies in which living cells or their components, such as enzymes, are used to cause desirable physical and chemical changes.

Bioprocessing to produce industrial chemicals (acetone and butanol) using microorganisms began during World War I. However, the growth of the petrochemical industry during World War II replaced the microbial production of industrial solvents, and industrial bioprocessing for bulk chemicals practically disappeared. When it was discovered how well biological processes could synthesize complex molecules, such as antibiotics, vitamins and enzymes, the industry was transformed from a high-volume, low-value industrial chemical producer into a low-volume, high-value producer. Bioprocessing offers opportunities to create new products and foods, treat and use wastes, and use renewable resources (biomass) for fuel. For instance, biomass energy (e.g., alcohol from grains and sugar, or methane from animal manures and other waste products) has received attention. In Brazil, alcohol fuel from the fermentation of sugar-cane juice is widely used.

3.2.3 Environmental Biotechnology

During most of its history, Canada's prosperity has been generated, in large measure, by its resource industries. For this reason, the third wave of biotechnology discoveries and technologies in the environmental domain is of particular significance and importance to Canadians. Following the first wave of biotechnology applications in health care and pharmaceuticals, and the second wave in agriculture and food, the third wave's domain focuses on the protection and restoration of the environment. Some would argue that biotechnology applications to restore and maintain our environment's integrity should be

a priority goal for Canada.

It has been suggested that, to be friendly to humans and the environment, industrial technologies of the future should have four key characteristics.

1. They should be based on renewable resources.
2. They should use "mild" production processes.
3. The resulting goods and services should be environmentally compatible.
4. Any generated waste should be recyclable.

Table 3.1

Examples of Biotechnological Developments Having a Significant Impact on Food Processing and Safety

Industrial Process/Ingredient	Underlying Science Disciplines	Underlying Process
Beverage sweeteners		
High-fructose corn syrup production	Immobilized saccharases and isomerase, microbial physiology, protein engineering	Conversion of low-value corn starch to higher-value sugar
Aspartame synthesis	Low water enzymology with proteinase	Synthesis of peptide bond by thermodynamics reversal of enzymic hydrolysis
Fats and oils		
Interesterification to upgrade low-value fractions, such as palm oil to cocoa butter equivalent	Low water enzymology with lipase	Fatty acid exchange on triglyceride glycerol backbone and solvent-free enzyme synthesis in heterogeneous systems
Improvement of functionality of fat shortenings		
Development of new biosurfactant emulsifiers		
Food proteins		
Production of single-cell protein	Microbial physiology, fermentation, bioreactor design and modelling, downstream processing, physics	Production of high-protein microbial biomass from low-value feedstock and conversion to textured protein
Protein hydrolysis/hydrolysates	Enzymology, protein/peptide chemistry	Conversion of proteins to highly flavoured peptide and amino acids for flavour-nutritional advantage and reduced allergenicity

Bread/baking		
Improved phospholipid emulsifiers in baking	Enzymology	Conversion of phospholipids to specific lysophospholipids
Improved yeast strains	rDNA technology	Optimize relationship between biological properties and process biological properties
Fungal amylase supplements	Microbial physiology, enzymology	Controlled starch hydrolysis during baking to improve texture
Dairy fermentations		
Cheese ripening enhancers	Enzymology, microbial physiology, genetic manipulation, microencapsulation technology	Acceleration of flavour and texture-generating reaction (protein hydrolysis, fat hydrolysis)
Coagulant technology	Microbial physiology, rDNA technology, protein engineering	Production of calf chymosin replacement in the form of fungal proteinases and cloned calf chymosin in heterologous microbial hosts
Starter cultures	Microbial selection, genetic manipulation, microbial physiology	Selection and stabilization of bacteriophage-resistant lactic acid bacteria for cheese and fermented milk
Biopreservation		
Production of natural antibiotics (e.g., nisin) and improvement of activity range	Microbial physiology, cellular biochemistry, protein engineering, bioseparations	Large-scale manufacture of microbially derived food preservatives
Enzymic suppression of fermentation defects	Microbial physiology, enzymology, microencapsulation technology, rDNA technology	Production, purification and delivery of antimicrobial (lytic) enzymes
Food analysis		
Detection of foreign proteins	Mab technology	Production and "packaging" of natural or synthetic recognition molecules to provide diagnostic kits
Detection of toxins	Biosensor technology	
Detection/identification of pathogens	Nucleic acid probe technology	

Source: Law, B.A. "Biotechnology in food manufacture." *Chemistry & Industry*, Vol..13, July 4, 1994, pp. 502-505.

Environmental biotechnology can contribute many of the technical options to achieve these goals. Although it is not the only technology capable of providing and maintaining a clean environment, it is an essential one and, in synergy with other tools, its importance is

growing. In the environmental biotechnology domain, there is a growing body of scientific conviction that there is still a large, unknown and little-exploited potential of naturally occurring microorganisms (NOMs) to contribute to the restoration and maintenance of the environment. Without contradicting this view, there may also be a need to use genetically engineered or modified microorganisms (GEMs) for the *in situ* degradation of the more recalcitrant pollutants, since the natural evolutionary processes might be too slow.

Second generation biotechnology is not just about genetic engineering. It also draws heavily on process technology, chemistry and classical engineering. In the environmental domain, bioreactor design and the use of immobilized cells are examples of technologies which have been developed, in parallel to genetic engineering, that should be classified as second generation biotechnology.

Present-day technologies have been directed at resolving localized environmental problems (e.g., an industrial effluent or contaminated site). In the future, more global issues may be addressed by biological solutions. For example, biological mechanisms exist for the removal of greenhouse and acid rain gases, for the production of environmentally acceptable energy sources and materials, and for resolving water shortages and desertification. At this time, the technologies to achieve these laudable goals are under development in laboratories. However, they have the capability of becoming major technologies.

The new biotechnologies for a clean environment have evolved against a background of traditional methods for waste treatment and in response to increasing environmental problems to be solved. There are a number of ways biotechnology can prevent or reduce environmental damage. These include:

- value-added processes which convert a waste stream into useful products;
- end-of-pipe processes where the waste stream is purified to the point that it can be released without harm into the environment;
- new biomaterials manufactured from materials with reduced environmental impact; and
- new biological processes that generate less waste.

Many good examples illustrate the value-added benefit of biotechnology processes in preventing environmental damage. For instance, a waste stream can be converted into value-added products such as methane (a biogas) or ethanol. Enzymes can be incorporated into animal feeds to increase the availability to the animal of dietary minerals while reducing the nutrient content of their waste. Processes use microorganisms to recover precious metals from waste streams.

Bear in mind that conventional chemical processes generate large amounts of waste and by-products through the use of high temperatures, extremes of pressure and a wide variety of highly reactive chemicals. In contrast, biotechnological processes generally occur at moderate temperatures and pressures. Enzymes or microorganisms are highly selective and the use of additional chemicals is minimal.

Bioleaching

In the mining industry, bioleaching is displacing the environmentally harmful practice of employing sulphuric acid to leach out metals from ores. Some acidophilic bacteria have the capacity to oxidize mineral sulphides. This releases metals from ores, concentrates or waste materials. However, for this biotechnology to be successful, the potentially toxic, liquid effluent from the bioprocess must be contained, recycled or treated.

The impact of biomining is entirely dependent on the combination of minerals and the local circumstances in which its use is contemplated. Nevertheless, there have been successful, commercial mineral-processing operations involving bacteria in Canada and globally. These processes are of three basic types:

- dump or heap leaching in which the bacterial activity causes the release of target metals (e.g., copper, uranium or gold) into percolating acid water;

- underground or *in situ* leaching of uranium (Being largely underground, this operation has greatly reduced environmental damage associated with uranium mining and surface tailings deposition.); and

- using bioreactors for processing high-value (e.g., gold-bearing) concentrates.

Biotechnology-Based, Environmental Detection and Monitoring Tools

Biotechnology research is now beginning to provide new environmental detection and monitoring tools. These technologies can assay pollution levels and provide early warning of acute pollution incidents. They can monitor and control industrial biotreatment processes — both bioreactors and *in situ* processes. Systems which combine biological and physico-chemical approaches are yielding sensitive and robust techniques for environmental measurement.

Biological surveillance using field surveys of whole ecosystems (detecting changes in species diversity and numbers) has been used for a long time to monitor chronic toxicity and bioaccumulation. Other examples of biological analysis are biological or biochemical oxygen demand (BOD) and biological methane potential (BMP). These tests are widely used by water authorities to assess the treatability and toxicity of industrial effluents. BOD is also used as a measure of biodegradable organic compounds in waste water. The conventional evaluation takes several days and is unsuitable for process control, but a more rapid estimation is possible using microbial sensors containing immobilized whole cells on oxygen electrodes.

Other more specific analyses used routinely by the water industry include the observation of chromosome damage to assess the risk from acute toxins. There is extensive use of biological activity for monitoring water quality, and there are standard procedures for assessing acute and chronic toxicity using a range of organisms.

Two general classes of biological detection methodology — biosensors and immunoassays — are just beginning to be commercialized for a few chemicals. In what seems to be a common path, these technologies were first developed for the health care industry but are increasingly being adapted for the detection of environmental pollutants. Biosensors are devices in which a biological agent has been immobilized and incorporated as the sensing element. Established bioassay technology is linked with transducer technology to give rapid, easy-to-use and often automated monitoring/analysis systems. The immunoassay is a powerful and versatile technique which has been successfully used in the measurement of a wide variety of compounds, primarily with medical applications. Immunoassays require highly specific antibodies which have the ability to recognize and bind to single compounds, small groups of related compounds or classes of compounds. The fundamental characteristics of each immunoassay are based on the specificity and binding affinity of these antibodies for the target compound (or compounds).

For the most part, biosensors and immunoassays are still in experimental development for environmental monitoring. Immunoassays have only recently been applied to the measurement of toxic compounds in the environment and the potential for using immunoassays to solve some of the problems of environmental measurement is just beginning to be realized.

In addition to the more traditional selection techniques and uses of special media, organisms may be detected and their numbers estimated by isolating their genetic material (DNA) and hybridizing this with probe sequences which have been labelled with either radioactive atoms or with chemiluminescent dyes. A major use of this technology has been to isolate organisms with specific properties, e.g., naphthalene-degrading bacteria in activated sludge and pathogenic species in dairy products.

The development of the polymerase chain reaction (PCR) in 1983 was a major methodological breakthrough in molecular biology. PCR permits the in-vitro replication of defined sequences of DNA to amplify gene segments. One application of this technique has been to enhance gene probe detection of specific gene sequences. In conjunction with DNA amplification using the PCR, detection kits for most species causing Legionnaire's Disease are now on the market.

Using rDNA technology, it is possible to insert genes, which will allow their subsequent detection, into microorganisms. These genes are known as reporter genes or genetic markers. This development has been central to advances in the understanding of microbial genetics and physiology. The most useful genetic markers are those associated with a biochemical assay that is both inexpensive and easy to perform. For instance, when an organism is exposed to a particular substrate, one such genetic marker will reveal itself by producing an insoluble blue dye. More recently, another genetic marker has been inserted into a number of organisms to enable their detection through emitted light. Environmental analysis using reporter genes is now a feasible technique (though, for most practical cases, viz., monitoring bioremediation, the use of a GEM marker will inevitably lead to an assessment under the *Canadian Environmental Protection Act* with concomitant information requirements and a waiting time for approval). Multiple reporters have been

inserted into a number of pesticide-degrading microbes to permit efficient monitoring after release into the environment.

Biopolymers

There is a continuing search for biopolymers to provide novel end uses. Thus far, biological polymers, flocculants and absorbents have been reported.

One bacterial polymer, polyhydroxybutyrate (PHB), a thermoplastic polyester, has been commercialized to alleviate problems associated with the disposal of non-biodegradable petroleum-based plastics. While the efficacy of this biodegradable product has yet to be fully validated, it would appear to offer a green alternative to some of the persistent organic packaging material still in use today.

Flocculants are widely used for waste treatment. However, synthetic polymeric flocculants, such as polyacrylamide, are not biodegradable and the monomer, acrylamide, is neurotoxic and a carcinogen. There is a clear demand for an environmentally friendly alternative.

Absorbent materials have many uses such as in baby diapers. A microbially produced bioabsorbent not only absorbs 1,000 times its own weight in water, but maintains its absorbency in highly saline environments.

Bioremediation Technologies

Biotreatment and bioremediation technologies can be understood in terms of the environmental "compartment" being treated (i.e., air and off-gases, soil and land, solid wastes, and wastewater, industrial effluents and drinking water).

In the air and off-gas compartment, peat and compost beds are often a cost-effective means for breaking down odours and simple volatile organic chemicals. However, existing biological systems for remediating industrial off-gases are often too slow or have short lifetimes because of the accumulation of by-products. Recent improvements in filter beds and biofilters, based on the use of synthetic substrates and selected organisms, may alter the economics for biotechnologies in this area.

Contamination of soil can be due to the presence of both organic and inorganic pollutants. Inorganic pollutants range from heavy metals to anions such as sulphate, while organic pollution extends from gross contamination of manufacturing sites (e.g., chemical plants or gas works) to trace pesticide contamination due to agriculture. Pollution can be acute (e.g., a spill) or chronic (e.g., leaking underground storage tanks). To date, the main impact of biotechnology on contaminated soil clean-up is in circumstances where the pollution is organic, because this soil is more open to microbial attack (Table 3.2). Use of microorganisms to remove inorganic and especially metallic pollutants is the subject of considerable research.

The principle underlying biodegradation as a tool in soil clean-up is the bringing of suitable microorganisms, various essential nutrients and, where necessary, air or oxygen into contact with the polluting material to optimize the conditions for breakdown. The microorganisms then use the pollutant as a substrate for growth converting it into a microbial biomass. Biological treatments, either *in situ* or *ex situ*, result in exponential degradation of the pollutants rather than straight line reduction. Thus, while zero levels of pollution are impossible to achieve, it is now possible to predict when a specific low level of contamination can be achieved.

Table 3.2

Potentially Suitable Chemicals for Bioremediation

Class	Example	Aerobic Process	Anaerobic Process
Monochlorinated aromatic compounds	Chlorobenzene	*	
Benzene, toluene, xylene		*	*
Non-halogenated phenolics and cresols	2-methyl-phenol	*	*
Polynuclear aromatic hydrocarbons	Creosote	*	
Alkanes and alkenes	Fuel oil	*	
Polychlorinated biphenyls	Trichlorobiphenyl	*	
Chlorophenols	Pentachlorophenol	*	*
Nitrogen heterocyclics	Pyridine	*	
Chlorinated solvents: Alkanes	Chloroform	*	*
Alkenes	Trichloroethylene	*	*

Source: U.S. Environmental Protection Agency.

Problems arise from the mechanical difficulties encountered trying to manipulate large volumes of soil to get the optimum conditions for microbial activity. Also, there is a huge variety of potentially polluting compounds some of which are relatively easy to degrade (e.g., petroleum hydrocarbons), others extremely difficult [e.g., polychlorinated biphenyl (PCBs)].

In situ soil and land biotreatments involve a number of techniques, both biological and non-biological, in which the soil is not (or is minimally) disturbed. *Ex situ* treatment requires the soil to be excavated and treated above ground either in piles or in specialized reactors. These latter procedures are easier to control than below-ground treatment. In Canada, bioremediation of land is becoming cost competitive with other physical methods including the least environmentally desirable alternative — the dig and haul approach. While the products of land bioremediation are generally considered harmless by the environmental biotechnology community, there is a consensus among regulators that rigorous monitoring and vigilance will be essential to prove this conclusion.

Specific *ex situ* land biotreatment technologies include composting, soil banking and slurry reactors, while *in situ* processes include nutrient solution injection (e.g., fertilizers), organism introduction and bioventing (where air is supplied both for microorganisms and as a carrier for volatile materials).

The simplest and preferred *in situ* processes involve the identification and stimulation (through nutrient addition) of the most appropriate indigenous organisms for biodegrading soil pollutants. Alternatively, organisms possessing specific biological potential can be added to the site.

The advantage of *in situ* treatments is that they do not disturb the site, an important implication for the future value of the land. If the site is in a sensitive area or is still operating while the remediation is taking place, then *in situ* remediation is the only option. However, harmful metabolites produced *in situ*, with higher solubilities than the original pollutants (e.g., polyaromatic hydrocarbons converted into phenols), can themselves pollute groundwater. Non-biological technologies, such as soil venting, are now well established for *in situ* soil clean-up, and these provide the main competition to biological technologies. A variant, known as bioventing, has air or oxygen trickled into soil layers at a rate that encourages natural organisms to metabolize pollutants. (The rate is not so rapid that volatile pollutants are stripped into the atmosphere.)

In situ bioremediation should not be considered complete until contamination levels have reached acceptable levels in the groundwater and in the soil, since a second clean-up operation may be needed when recontamination of the groundwater occurs as a result of the dissolution of residual contamination in the soil.

In another technique, known as air sparging, air injected into the saturated zone beneath the area of contamination causes volatile organic compounds (VOCs) to partition from the dissolved or adsorbed phase into the air phase, where they are transported into the vadose zone as soil vapours and are captured and removed by a vapour collection system. Air sparging has been used in the enhanced remediation of gasoline-contaminated saturated soils and groundwater. Air sparging also elevates the dissolved oxygen concentration in the groundwater, enhancing the biodegradation of less volatile, higher molecular-weight compounds.

The technology of bioremediating contaminated land is beginning to come of age. There have been enough successes in Canada, the United States and Europe to validate a number of the outlined techniques. In the United States, some of the most publicized examples involve Superfund sites.

No one method will provide an answer, and all techniques have their place. In terms of competition with other technologies, bioremediation has an advantage in that, in the majority of situations, it is the cheapest option — with the exception of removing the contaminated material to a landfill site. U.S. legislation restricting land disposal of hazardous waste and the financial and legal liabilities arising from the Superfund have allowed the development of sophisticated bioremediation technologies. The same situation is occurring in Germany, the Netherlands and the Scandinavian countries. In Canada and the United Kingdom, it is still cheaper to take contaminated material to landfills which means that, in most cases, bioremediation is not competitive. This is changing rapidly in Canada because of the *Canadian Environmental Protection Act* regulations and increasing landfill costs.

The essential requirements for any remediation process are that it be reliable (in terms of the results to be achieved) and predictable. Polluted sites are very complex and the choice of technology is, therefore, very site-specific. As a new technology, bioremediation is in a difficult situation: results are required from treated sites to give it a predictive capacity but contractors hesitate to use it until its reliability is proven. Until this changes, site-characterization costs, while applying to all remediation technologies, may be particularly disadvantageous to bioremediation methods.

The main problem with bioremediation is that it is time consuming, tieing up land capital and preventing land reuse. There is also a lack of scientific understanding of, for example, degradative pathways (Table 3.3). Although virtually all organic materials are degradable to some degree, the ease of breakdown can vary radically, and much work is needed to isolate strains of microorganisms to degrade recalcitrant pollutants to harmless end products. Biotechnology does have the advantage that, because microorganisms are used to break down the organic matter, the end products are minerals, carbon dioxide, water and biomass. The most important other remediation technology that achieves a similar breakdown is incineration. All other technologies concentrate the material without changing its form.

Table 3.3

Advantages and Disadvantages of Bioremediation

Advantages:

- An ecologically sound, "natural" process.
- Destroys rather than transfers contaminants to other media.
- Usually less expensive than alternatives.
- Can often be accomplished where the problem is located.

Disadvantages:

- Research is needed to develop appropriate technologies.
- Often takes longer than other remedial actions.
- By-products, which may be toxic, can sometimes be formed.

Source: U.S. Environmental Protection Agency.

Solid waste treatment aims to convert waste into a safer, less toxic, more stable material which can be used or disposed of. Techniques include deposition in landfills, composting (an aerobic process) in open piles or bioreactors, and anaerobic digestion of solids to

convert their organic content into usable methane. With source-separated solid organics, a number of biotechnological processes are being introduced, which can address an estimated 30 percent of the total solid waste.

Traditionally, wastewater and industrial effluents were biotreated to reduce organic matter. Now, there is a recognized need for technologies that can remove specific pollutants. Priority targets include nitrogen, phosphorus, heavy metals and chlorinated compounds. Both aerobic and anaerobic processes and fixed bed and suspended reactor systems are used for water treatment. The appropriate choice depends on the quantity, concentration and nature of the pollutants present and on the area available for the technology. With every lowering of pollutant target levels, physical processes, in combination with adsorption and biodegradation using selected organisms, will be used more and more to treat recalcitrant compounds.

Experts note that wastewater treatment plants currently in use are essentially operated on a black box principle and lack reliability and performance. Enhancements in aqueous effluent treatment have arisen more through improvements in reactor configuration. Individual processes need to be optimized and controlled, e.g., adjusting intake quantity and/or quality and modifying the microbial community.

Biotechnology's Role in Emerging Global Environmental Problems

Pollutants that are widely spread through the atmosphere are an emerging environmental problem, as is the depletion of scarce resources. These problems transcend national boundaries. The massive use of fossil fuels has led to increased carbon dioxide emissions. Industrial activity has led to production of other greenhouse and ozone-depleting gases such as chlorofluorocarbons (CFCs), e.g., Freon. Increasing amounts of methane are being released as a result of rice production and cattle breeding. Such global changes may emerge as major problems of the next century unless preventive measures are implemented and environmentally benign materials developed to replace those chemicals that have caused global environmental deterioration.

The 21st century will see the possibilities of applying biotechnology to global, in addition to local, environmental threats. Three have been identified which might be resolved by biotechnology: deteriorating atmospheric quality (greenhouse and acid rain gases), depletion of natural resources (fuels, materials), and water shortage and desertification.

Carbon dioxide may be removed or "fixed" by green plants, algae and bacteria to improve atmospheric quality. Some fossil fuels may be replaced by renewable fuels produced by plants or microorganisms. Acid rain has many causes, particularly the emission of sulphur and nitrogen gases from power plants, automobiles, animal housing and wastewater treatment. Experts suggest that research priorities for acid gas remediation should include the development of bio-filters for the removal of organohalogens, sulphur and nitrogen compounds from stationary point sources. Further, they suggest seeking a fundamental understanding of the natural ecosystems of forests to adjust them and protect the forests.

Research into the interaction of organisms, plants and the environment, in selected ecosystems (e.g., paddy fields) is required to modify them to achieve specific ends (viz., reduced methane emissions).

Natural resources (i.e., forests, water, fossil fuels and metals) are being depleted at an unsustainable rate. Biotechnology may make renewable resources more economical and aid in resource recycling. Bioprocesses may increasingly replace conventional processes, especially in the chemical industry. Research into organisms producing polymer precursors is needed. Where possible, replacement of existing materials derived from fossil fuels with renewable materials should be pursued. Metals are released into the environment from industrial and domestic sources and following waste treatment. Since these metals cannot be destroyed by physical or biological treatments, experts call for the development of biological processes to recover metals and make them available for recycling.

The large-scale use of fossil water, changing climate and increased water consumption as a result of demographic changes are putting ever-mounting pressure on water resources. Also, partly as a consequence of human activity, deserts are increasing on every continent. By helping to clean up large bodies of water, we could make more water available. In this field, we need research into the mechanisms used by plants to survive in low-water and brackish-water conditions with the aim of developing superior plants for these conditions. Research is needed on super-absorbent biopolymers as water-retaining materials in desert conditions, and on the selection and development of plants and microorganisms, with an understanding of the ecosystems, which will improve the quality of water by removing inorganic pollutants (e.g., nitrogen, phosphorus and metals).

Economic Considerations in Environmental Biotechnology

One of the earliest and widest applications of traditional biotechnology was the treatment of wastewater in facilities built in the 19th century to safeguard public health in urban areas and reduce water pollution. Given this head start, it seems unusual that applications in environmental biotechnology did not receive much attention in the early 1970s when health sector applications followed by agri-food technologies rose quickly to the forefront. The impact of environmental biotechnology applications was not felt until the mid-1980s. Some experts believe the reason for this delay lies in the nature of biotechnology development itself. This development relies on the work of university and research institute scientists and follows traditional basic research interests.

Biotechnology development takes place along a "science push" to "market pull" trajectory. The term "science push" connotes technological developments driven largely by scientific research initiatives. Perhaps more than any other major technology of the 20th century, biotechnology, which harnesses the power of living organisms and puts them to good use, was born in universities and nurtured by scientists with traditional scientific motivations. Its trajectory was first determined by little else than scientific competition and the excitement which the prospect of great discoveries creates in the human mind.

Environmental biotechnology also faced a glamour problem in its inability to compete with either medical or agricultural biotechnology. Scientists, students and research funds were more easily attracted to the new molecular biology which promised to cure dreaded diseases or to address food requirements for developing countries over novel means to treat water sewage and remediate polluted lands.

The glamour problem (or lack of "science push"), was not the only reason for a slow start in the development of environmental biotechnologies. The simple fact is that there were existing, large, accessible and lucrative markets for health care and agri-food products (a "market pull") in all industrialized countries, while there were few if any corresponding markets for environmental biotech products. Legislation, policies and regulations have accelerated the creation of these latter markets and have had the effect of internalizing previously unrecognized (or unaccepted) external costs of environmental degradation. Alone perhaps among the three waves, environmental biotechnology has required the public's awareness and concern to create legislation which would stimulate the development of domestic and global markets. This same public concern for environmental health and safety could now inhibit the development of a responsible and globally competitive Canadian environmental biotechnology industry through costly biotechnology environmental regulations. Canada's proposed regulations are examined in Chapter 5.

Legislation and regulation can stimulate the development of environmental biotechnology (and other remediation) markets. However, these governmental powers will come to naught without enforcement and control, and without intergovernmental consistency of application. Beyond these legislative measures, governments can assist through the provision of R&D money and, as noted above, the federal government is increasing its investment in environmental biotechnologies both in absolute terms, as a share of its total expenditures in biotechnology, and at a faster rate than for other biotech domains.

Five criteria for development and diffusion of new technologies in a society have been characterized:

- a new range of technically improved products and processes;
- cost reductions for many of these;
- social and political acceptability;
- environmental acceptability; and
- pervasive effects throughout the economic system.

In 1985 and after, when comparisons were first attempted, the case for biotechnology was not yet clear-cut. It satisfied the first criterion, at least partly. It did not fully satisfy the second criterion as comparative costs of biotechnology remained high in certain sectors such as health care. Also, the problems of social and environmental acceptance encountered by some biotechnology applications were quite obvious. With regards to the fifth criterion, biotechnology was seen to have diffused far more than most other technologies (information technology excepted) because of the long history of the more traditional biotechnologies and their applications across many societal sectors. The view, on balance, from the mid-

1980s was that biotechnology would not become a predominant technology in this century for many sectors and processes. Achieving a level in which macro-economic effects would begin to be felt [viz., gross domestic product (GDP) growth, employment and investment] was projected to take at least one generation, which meant by around the year 2010.

A more recent appraisal yields the following conclusions. While the number of environmental biotechnology products has increased quickly during the last five years, the field still suffers from the black box problem, i.e., the working of biological processes, particularly in bioremediation, is scientifically not well understood. Neither is the feasibility, reliability and predictability of these methods well-characterized scientifically. Some experts believe that a concerted R&D effort here will overcome these disadvantages in about 10 years.

There is no question that bioremediation is emerging as a cheaper, possibly much cheaper, technology than competing alternatives. Biotechnology has suffered with respect to political and social acceptability (inextricably linked criteria) because of its association, in the public's mind, with genetic engineering. Capitalizing on a separation in the public's perception between environmental biotechnologies as a "natural" technology working effectively with NOMs will provide the means for overcoming this obstacle and promoting the diffusion of this technology. This will also promote environmental acceptability. Last, the key to achieving pervasiveness of environmental biotechnologies throughout society may, in some expert's view, depend on linking the technology to the emerging problems of the 21st century, e.g., greenhouse effect, desertification, water shortages and resource depletion.

3.3 Market Potential

In its brief history, second generation biotechnology has diffused into many sectors of the economy. We have reviewed the current science to identify emerging technologies and identified the likely major *visible* impacts in the future. The size of these impacts will depend on consumer acceptance. The current evidence suggests that this acceptance will be more forthcoming in the health care, environmental and resource sectors, and will be much harder to achieve in the agri-food sector. In this section, we look more closely at resource sectors of the Canadian economy where biotechnology will provide less visible but undoubtedly important value-added technologies to enhance the competitive advantage of Canadian export products.

A good example is provided by a diagnostic technology (DNA probe) in the form of a blood test for a genetic defect in hogs known as Porcine Stress Syndrome (PSS). Pigs with this genetic condition are more susceptible to heart failure when exposed to stress from transportation, slaughter, fighting, mating, vigorous exercise or even hot or humid weather. Researchers at the universities of Toronto and Guelph developed the technology which was licensed by the University of Toronto's Innovations Foundation to the Canadian Pork Council. This agreement will lead, in turn, to enhancements in the quality of meat produced by the Canadian pork industry through the superior appearance and processing yields which

will become possible with pork from PSS-free pigs. This basic discovery coupled with a successful technology transfer provides one example of the value-added benefits of biotechnology, in this instance, through the Canadian pork industry to the Canadian economy.[98]

Discussions with agbio representatives have underlined the strategic importance of developing insect-resistant and herbicide-tolerant food commodities, especially in product categories where Canada enjoys world leadership (e.g., canola). The country should be building on this commodity base by developing, for example, canola oil with genetic traits to fill global niche markets. In this example, Canada needs a canola seed-crushing facility. It could be financed over a 10-to-15-year time frame. Since venture capital firms will not consider this longer time frame, government financing (with appropriate lease or buy-back provisions) should be provided to reduce the risk to the point where the investment becomes attractive to capital markets. The importance of industry management of such enterprises (and the government remaining a patient, arm's length participant) were also stressed.

Table 3.4 shows the characteristics which rDNA technology will be developing in transgenic plants that are important to Canada's agricultural sector.

- In the next one or two years, Canadian agbio will see the emergence of hybrid canola seed (with 15 percent to 20 percent greater oil yields).

- In two to five years, there will be even higher-quality canolas, as well as insect-resistant and herbicide-tolerant potatoes, corn and so on.

- In five to 10 years, higher-quality, insectant-resistant and herbicide-tolerant cereals will be produced with starch modifications.

- Seed treatments in the form of microorganism products of fermentation will appear in the near future as biofertilizers, bioherbicides and biopesticides. These liquid treatments will be added to seed mixes in the seeding augurs used to till the seed into the soil.

- Other agbio technologies currently in development include nitrogen-fixating legumes, rhyzobium technology, bacillus thuringiensis (a natural microbial species with biopesticide applications), additional seed treatments (to enhance phosphate uptake from soil and reduce reliance on phosphate fertilizers) and hardy winter wheat.

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[98] University of Toronto Innovations Foundation. "Innovations Foundation licenses technology to Canadian Pork Council." IF News Release, Toronto, Canada, February 22, 1993

Table 3.4

Important Characteristics of Transgenic Plants in Food Technology

Plant	Resistance			Tolerance		Nutritional Value	Controlled Ripening
	Insect	Virus	Microorganism	Herbicide	Stress		
Apple	+						
Bean		+					
Broccoli			Fungi				
Canola	+	+	Fungi	+	Heat	Low saturated fat, oil composition, seed protein	
Corn	+	+	Fungi	+		Amino acid content, oil composition	
Cucumber		+					
Grape		+					
Melon		+	Fungi	+			
Oilseed plants						High laurate oils	
Pea							+
Pepper			Fungi				+
Potato	+	+	Bacteria, fungi	+	+	Solids and dry matter	
Rapeseed	+			+		Fatty acid content	
Soybean				+		Amino acid and fatty acid content	
Squash		+					
Strawberry	+			+			
Sugar beet		+		+			
Sunflower						Amino acid content	
Tomato	+	+	Bacteria, fungi	+	Free-zing	Solids and dry matter	+

Source: Dörnenburg, H. and C. Lang-Hinrichs. "Genetic engineering in food biotechnology." *Chemistry & Industry*, Vol.13, July 4, 1994, pp. 506-510.

A 1990 report[99] identified 11 biotechnology mechanisms for developing products to meet a number of animal production objectives (productivity, feed efficiency, use of alternative feeds, product composition, disease control/animal health, carcass quality, reproductive management and performance). These mechanisms were identified as follows:

- control of metabolic pathway through immunological or chemical mechanisms;
- enhanced reproductive capability of superior animals through embryo sexing, splitting, preservation and cloning;
- transgenic manipulation to obtain or enhance desired traits;
- microbial enhancement of feeds;

[99] Deloitte & Touche, *A study of strategic opportunities for Canadian biotechnology in animal husbandry products.* Phase I and II reports, prepared in June 1990 and January 1991 for Industry, Science and Technology Canada (ISTC).

- genetically engineered microbes and chemicals applied internally or to the feed to enhance palatability, nutrition or digestibility of alternative feeds;

- bio-engineering of feedstuffs or feed additives to enhance meat characteristics;

- engineered vaccines/antigens which cannot currently be produced economically or in pure enough form;

- gene modification of microbes to produce chemicals to control disease;

- transgenic alteration to enhance an animal's ability to react to, or resist, the disease organism or causative factor; and

- development of gene markers to aid in conventional breeding for resistance.[100]

The report identified significant market opportunities for a number of biotechnologies:

- high efficiency vaccines and diagnostic products (for shipping fever, pleuropneumonia, infectious bovine rhinotracheitis and baby pig scours);
- probiotic organisms or their relevant substrates (e.g., as feed additives); and
- immunological approaches (e.g., to produce low-fat hogs and beef cattle, and low-fat dairy products).

A number of Canadian NBFs and subsidiaries of multinationals are working in collaboration with researchers at the universities of Guelph and Saskatchewan to develop technologies within these identified areas.

Another promising area is anti-ideotopic antibodies which mimic hormones, enzymes, toxins, microbes and receptors. The implications for their use are enormous as they can potentially block or enhance virtually any process that is affected by the product which they are mimicking. Potential uses for the technique, sometimes called "biopharming," include passive immunity, physiological regulation, therapy, drug design and delivery.

In forest biotechnology, Canada's efforts rate among the most advanced research programs in the world.

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[100] Deloitte & Touche, *A study of strategic opportunities for Canadian biotechnology in animal husbandry products.* Phase I and II reports, prepared in June 1990 and January 1991 for Industry, Science and Technology Canada (ISTC).

In tissue culture, there are no programs of comparable quality or impact in the world to those in Canada. Tissue culture, especially the new developments with conifers in somatic embryogenesis, has two extremely important roles to play in the overall strategy for improvement and conservation of forest trees through forest genetic programs. First, through the use of tissue culture, genetically improved varieties of trees can become part of a reforestation program in as little as three to five years (versus the conventional 15 to 20 years of field testing). Second, tissue culture allows rapid change in the genetic composition of trees used in reforestation techniques. Through cryopreservation techniques developed by Forestry Canada and the National Research Council, it is now possible to capture what geneticists call the "non-additive genetic variation" component and produce elite trees. Commercial implementation of this technology awaits successful technology transfer to private industry and the provinces.[101]

In the pulp and paper sector, biological wastewater treatment is applied to mills, especially kraft mills, to reduce biological oxygen demand, toxicity and suspended solids, and decrease chloroorganic discharges. Enzyme treatments facilitate kraft pulp bleaching and decrease pitch deposition in papermaking and, in conjunction with cellulase, increase dewatering rates of recycled furnish during papermaking. Applied research on biological bleaching and in biomechanical pulping with fungi is proceeding. Basic research is proceeding with enzymes to produce delignification of wood or pulp. The successful application of technologies has been facilitated by low cost and by legislation; and through supplier companies in the application of enzyme treatments. [102]

In the mining sector, a number of biotechnology applications are under development or have been successfully demonstrated:

- bacterial leaching of uranium (commercially demonstrated at Denison Mines);
- bacterial leaching of copper and zinc;
- bacterial degradation of a pollutant produced during aluminum refining;
- biorecovery of selenium from smelter effluents;
- biological mitigation of acid mine drainage (field tested at Inco and Denison sites);
- biodegradation of de-icing fluids and urea;
- biodegradation of cyanide in mill effluents;
- biosorption of uranium from dilute solutions;
- microbial exopolymer plugging of mine tailings; and
- bacterial pre-oxidation of refractory gold ores.[103]

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101 *Biotechnology in Forestry*. Report to NBAC by Forestry Canada, September 1990.

102 *Biotechnology in the Pulp and Paper Industry.* Report to National Biotechnology Advisory Committee (NBAC) by P&PRI Canada, April 1991.

103 Jeffery, W.J. *Biotechnology applications and trends in the mineral and energy sectors.* Report to NBAC by Mining Industry Technology Council of Canada (MITEC), December 1990.

Fossil fuel applications of biotechnology include:

- microbial plugging of an oil reservoir to prevent watering out of the wells during secondary oil recovery;
- microbial degradation of refinery sludges;
- microbial plugging of porous or fractured zones during drilling for oil;
- microbial dewaxing of oil wells;
- biofouling and biocorrosion of process lines; and
- microbial degradation of coal tar.[104]

In the mining and energy sectors, biotechnology will make its most significant impact in the short term by economically resolving environmental problems resulting from industrial activity. Major projects will be initiated in areas such as:

- the bioremediation of mine sites once they close;
- bioremediation of oil spills;
- bioremediation of tar ponds associated with coking plants;
- *in situ* biological treatment of contaminated aquifers and soils;
- biorecovery or biomineralization of metal ions in industrial effluents; and
- the development of biological processes to degrade organic reagents associated with industrial effluents.

The development of new mineral or fossil fuel biotechnological processes to optimize mineral or energy recovery will develop more slowly and is an area of long-term research.[105]

3.4 Canadian Biotechnology Opportunities

Forecasting is made more difficult by a number of facts which characterize the science itself (e.g., rapid technological obsolesence and risk dogging every product development stage) and by the absence of a coherent and co-ordinated strategy in this country which would lend greater predictability to the industry's future. Having said this, five and 10-year forecasts are provided for sectors of the Canadian biotechnology industry.

For several compelling reasons, the industry will not be able to sustain its five-year growth rate in sales of 24 percent per year (Table 1.8). Our survey confirmed that the Canadian industry ranks lack of financing as the number one barrier to market entry (Table 4.2). Consider this finding in relation to Canadian and American investment markets. Five years ago, demand by investors exceeded the supply of available biotechnology companies in which to invest. The situation reversed itself in 1994.

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104 Ibid

105 Ibid

There are now 40 private Canadian health care biotechnology firms in Canada pursuing recombinant product development (Table 1.17). Over the next five to 10 years, these firms will be seeking large infusions of capital to commercialize their products (recall that a therapeutic bioproduct's development cost is conservatively estimated to be US$125 million). Some may have ambitions to become fully integrated pharmaceutical companies (FIPCOs) — with possible development costs ranging from US$600 million to US$1 billion. Clearly, this competition for capital will lead to a consolidation of the Canadian health care biotechnology industry in the form of mergers, buyouts and, it is hoped, few business failures (which would dampen investor confidence even more than at present) over the next several years.

The market for biopharmaceuticals is becoming increasing tough to sell into. And the perception is that they are very expensive and, in some instances, not very cost effective. Some recently introduced drugs have clearly added value even though they are enormously expensive. Others, however, have provided only a marginal benefit, also at great cost. For such bioproducts, the pharmacoeconomic analyses show large costs per unit of benefit. The insurer (Canadian provincial drug formulary managers or U.S.-managed care organization managers) would consider these benefits insignificant and would continue to recommend standard treatment. However, the patient would want those benefits, and the drug maker would argue that aggregate health care benefits, although costly, would be significant.

Perhaps the most important factor affecting growth in the Canadian biotechnology industry will be Canada's underlying fiscal climate with upward pressure on interest rates from the international competition for capital markets.

- For all these reasons, we are of the opinion that the most likely 10-year trend growth rate for the health care biotechnology sector will be 10 percent (compared with a previous four-year average of 27 percent). We have put upper and lower bounds of 15 percent and 5 percent on this trend to define high and low-growth scenarios. All three scenarios assume the inevitability of a rationalization within the sector.

On the other hand, we are encouraged about growth prospects in the resource sectors where Canada continues to enjoy a global competitive advantage and there is a growing and significant "market pull" assisting the biotechnology "science push."

- With a coherent national strategy, the agbio sector will exceed its previous four-year growth average (16 percent per year) in our most likely scenario over the next 10 years and should average 20 percent per year. The upper and lower bounds for this growth path are 30 percent and 10 percent and reflect the possibility that, on one hand, world food demand may expand more rapidly than expected and, on the other, that the agbio sector will also be impeded by a poor investment climate and consumer resistance.

- The Canadian environment and resource sectors should continue to surge in response to world demand for bioremediation especially given national expertise in these sectors. The sectors are forecast to grow from their relatively small sales bases

in 1993 of $66.7 million and $29.8 million respectively at a 40-percent-per-year clip over the next 10 years. This most likely scenario has upper and lower bounds of 50 percent and 25 percent respectively.

The most likely scenario for the Canadian biotechnology industry is to tax annual growth expected to average 17.4 percent per year over the next five to 10 years. The low and high-growth scenarios yield trend forecasts averaging 8.7 percent and 25.5 percent per year respectively. Table 3.5 shows the most likely Canadian sales forecasts for 1998 (five years) and 2003 (10 years).

Table 3.5

Low, Median and High-Growth Forecasts of Sales ($M) by Sector for the Canadian Biotechnology Community 1993-2003

Sector	1993	1998	2003	Annual Growth: 1993-2003
Median-Growth Scenario				
Agri-food	$688.0	$1,712.0	$4,259.9	20%
Environment	66.7	358.7	1,929.3	40%
Health Care	1,310.7	2,110.9	3,399.6	10%
Resource	29.8	160.3	862.0	40%
Total	**$2,095.2**	**$4,341.9**	**$10,450.8**	**17.4%**
Low-Growth Scenario				
Agri-food	$688.0	$1,108	$1,784	10%
Environment	66.7	204	621	25%
Health Care	1,310.7	1,673	2,135	5%
Resource	29.8	91	278	25%
Total	**$2,095.2**	**$3,076**	**$4,818**	**8.7%**
High-Growth Scenario				
Agri-food	$688.0	2,554	9,485	30%
Environment	66.7	507	3,846	50%
Health Care	1,310.7	2,636	5,303	15%
Resource	29.8	226	1,718	50%
Total	**$2,095.2**	**$5,923**	**$20,352**	**25.5%**

Under the median-growth scenario:

- Health care's share of Canadian biotechnology sales will decline from 63 percent and first place in 1993 to 33 percent and second place by 2003.
- Agri-food will switch places with health care, moving its market share from 33 percent to 41 percent.
- Environment's share will climb from 3 percent to 18 percent.

- Resources' share will increase from 1.4 percent to 8.2 percent.

Forecasting employment growth in Canadian biotechnology is made difficult by the vagaries of labour markets in this country. Our survey revealed productivity improvements in the natural product business of the agri-food biotechnology industry, and in the recombinant product business of the health care sector (Table 1.16). There is bound to be a developmental cycle to productivity gains in various biotechnology sectors with the least developed showing the worst productivity (i.e., low sales and large employment levels). The expectation is that productivity will improve as business activity picks up in agri-food, environment and the resource sectors. With this reasoning and the most likely sales growth forecast in mind, larger aggregate employment growth in the next five years (i.e., greater than 17 percent per year) can be expected followed by lower growth in the succeeding five-year period (i.e., less than 17 percent per year). This would lead to likely employment levels in Canadian biotechnology in 10 years (the year 2003) of around 116,000, or roughly a fivefold increase in the current number of full-time equivalent (FTE) jobs.

CHAPTER 4

COMMERCIALIZATION OF BIOTECHNOLOGY PRODUCTS

This chapter explores the effects of Canadian policies relating to intellectual property (IP) protection and environmental regulations from the perspective of Canadian biotechnology companies seeking to commercialize products for a global market.

4.1 Market Entry into the Biotechnology Industry

This section reviews the results from our survey of the Canadian biotechnology industry, and identifies and gives a priority to the key reasons for a firm's entry into the market. Start-up barriers are also identified. The results are shown in tables 4.1 and 4.2.

Table 4.1

Key Reasons for Market Entry by a Canadian Biotechnology Firm by Sector and Size of Firm

	Sector (%)						Size of Firm (%)				
Key Reasons	**Hlth**	**Agri**	**Envt**	**Sup**	**Res'ch**	**Res'ce**	**1+**	**11+**	**26+**	**101**	**Tota**
Market opportunity or demand	45	61	68	38	47	53	52	36	47	52	49
In-house expertise	25	7	24	30	24	22	22	32	28	22	24
Access to proprietary knowledge	16	12	10	16	5	7	9	13	25	5	12
Access to research facilities	21		4		5	11	8	4	4	11	7
Spinoff opportunity	4	6	6	6		5	5	3	8		5
Positive regulatory environment	5		4	3	8	5	2	10		17	4
Public sector financing/incentives	9			6	3		2	10	8		4
Part of firm's mandate				2	25		3	6		10	4
Private sector financing			6	5	3		3	3	4		3
Access to raw materials	6					7	2	2	6		2
Availability of production facilities				3		7	1		4		2

Notes:
Respondents were asked an open-ended question out of which these choices emerged.
Abbreviations: Hlth = Health Care, Agri = Agri-food, Envt= Environment, Supp = Suppliers, Res'ch = Research, Res'ce = Resources.

- Of respondents across all biotechnology sectors and firm sizes, 49 percent ranked market opportunity or demand as the most important reason for seeking market entry. Other reasons included the availability of in-house expertise (24 percent), access to proprietary knowledge (12 percent) and access to research facilities (7 percent).

- Among health care firms, market opportunity or demand was most important (45 percent), in-house expertise was second in importance (25 percent), closely followed by access to research facilities (21 percent) and proprietary knowledge (16 percent).

- Research firm respondents singled out market opportunity or demand as the most important (47 percent) and their mandates as the second most important reason (25 percent) for entering the market.

- Only a small perentage of respondents felt that a positive regulatory environment (4 percent) and public sector financing or incentives (4 percent) were factors in seeking market entry.

Survey respondents identified the major barriers their companies experienced when entering the market (Table 4.2).

- Lack of financing was the biggest barrier of all. This was identified as the major barrier by 31 percent of all respondents, including 44 percent of research firms, 42 percent of resource firms and 39 percent of health care firms. Agricultural sector respondents ranked lack of training as fourth in importance behind lack of market acceptance and Canadian and foreign regulatory barriers, while environmental firm respondents ranked it second behind lack of market acceptance. Lack of financing was the highest-ranked barrier for all sizes of firms save the intermediate-size firms (26-100 employees) for which it ranked second behind lack of market acceptance. Given the current investment climate for biotechnology, the perception by agbio respondents that financing is less of a barrier bodes well for that sector's growth prospects.

Table 4.2

Major Barriers Faced by a Canadian Biotechnology Firm Entering the Market (by sector and size of firm)

	Sector (%)						Size of Firm (%)				
Market Barriers	**Hlth**	**Agri**	**Envt**	**Sup**	**Res'ch**	**Res'c**	**1+**	**11+**	**26+**	**101**	**Tota**
Lack of financing	39	13	21	28	44	42	35	20	27	33	31
Lack of market acceptance	22	25	35	15	9	30	22	7	32	17	21
Canadian regulatory barriers	16	24	14	6	5	16	12	11	12	11	13
Labour availability	10	6	4	4	8	17	7	16	8		12
Competition	4		9	7		14	5	17	4		7
Product development risk	3			7		4	4	3	4		6
Foreign regulatory barriers		14		3				7	8		3
Distance to markets		6		4			4	3			2
Raw material availability	2					13	1	9			2
Insufficient regulation and enforcement	3		9				2	4			2
Lack of regulatory knowledge	3		8				2	4			2
Biotech equipment availability			3		10		2	3			2
Insufficient biotech reference material		7	6				1		4		2
No confidence in Canadian producers				2			1				1

Notes:
Respondents were asked an open-ended question out of which these choices emerged.
Abbreviations: Hlth = Health Care, Agri = Agri-food, Envt= Environment, Supp = Suppliers, Res'ch = Research, Res'ce = Resources.

- Canadian regulatory barriers ranked third in importance overall, but they were second in importance for the agbio sector as reflected in comments received during interviews.

- IP protection was not perceived as a barrier by any respondents. This view probably stems from comments repeatedly expressed by health care respondents during interviews that the Canadian market ranks either third or fourth in importance behind U.S., European and Japanese markets. For health care biotechnology firms in particular, product acceptance and IP protection in these countries are far more important than domestic approval and protection. Sales penetration into large industrialized, and therefore lucrative, markets dominates the agenda of this sector.

Additional barriers were identified as significant by a few smaller environmental firms. These included:

- insufficient regulation and enforcement;
- a lack of regulatory knowledge;
- unavailability of biotechnology equipment; and
- insufficient biotechnology reference material.

Along with resource sector firms, these respondents recognize that stringent Canadian environmental regulatory requirements create a market opportunity and enable the development of technologies that can be exported into foreign markets. This topic is addressed more fully in Chapter 5.

Capital is the principal start-up barrier according to interviews with IP practitioners and members of the Canadian biotechnology industry, and a review of recent literature on IP protection in Canada. Access to capital affects IP protection in that if a biotechnology firm does not have adequate cash inflow, it will be unable to seek and maintain IP protection. Conversely, if a biotechnology firm does not have strong patent protection, it will be unable to raise capital (through private or public market placements, or through licence, distribution, joint venture or strategic alliance agreements).[106] Access to investment capital is contingent on the ownership of or right to use patentable technology according to interviews with representatives of Canada's financial community. They noted that a Canadian biotechnology firm's ability to raise capital decreases dramatically when the firm lacks a strong patent position.

Maintaining confidentiality of inventions was often a start-up barrier. This comment was made by patent practitioners who work with universities and research institutes. There is pressure on academics to publish their work before the university or research institute files a patent application covering the work. However, in many countries, an invention cannot be disclosed publicly before an applicant files a patent application for the invention. Thus,

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[106] Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." *Canadian Intellectual Property Review*, Vol. 10, 1993, p. 347

publications by academics can jeopardize their ability to commercialize or license their inventions. In Canada and the United States, there is a one-year grace period within which inventors may disclose (i.e., publish in learned journals) their inventions and still file patent applications to protect their discoveries.

Before entering into agreements with universities or research institutes, potential partners require that:

- the inventions of universities and research institutes be patentable; and
- such inventions be confidential and remain confidential until the commercial partners are prepared to disclose publicly such inventions.

Practitioners interviewed for this study recommended that scientists at universities and research institutes learn the importance of IP protection and confidentiality of inventions to assist the universities and research institutes in commercializing their biotechnology inventions.

A senior university official responsible for technology transfer at his institution remarked that academics face a real financial barrier when considering patents for their discoveries. IP protection gains value with the size of the market in which that protection is obtained. Obtaining protection in the major markets — the United States, Europe, Japan and Canada — is beyond the financial reach of these inventors and, usually, their institutions. This individual identified the need for start-up capital at this vital entry point as a necessary precondition for commercializing the underlying technology.

Furthermore, multinational firms will not consider a strategic alliance in the absence of IP protection.

Another interviewee remarked that scientists were anxious to obtain and maintain government funding. Scientists' perceptions are that the government is more likely to fund a scientist's work if that scientist has many publications. Therefore, scientists are principally concerned about publishing their work, not protecting it.

4.2 Stages of Biotechnology Commercialization

Biotechnology products, such as therapeutic biopharmaceuticals, take many years to commercialize. Development activity stretches over a number of stages:

- the basic research leading to a discovery;

- various types of applied or preclinical research (involving the synthesis and extraction of the molecular entity, toxicology and safety testing using animals, and related activities);

- clinical trials (i.e., to assess safety and efficacy, pharmacokinetics, bioavailability, dosage formulation and stability testing);

- regulatory applications (both to begin human studies and to receive final approval to market the product); and

- production, marketing and distribution.

Canadian firms developing health care biotechnology products experience regulatory delays throughout the world. Interviews with representatives of these firms and of Canada's financial community indicated that regulatory delays affect a firm's IP strategy and its ability to raise capital. These firms tend to postpone their request for examination of their Canadian patent applications until:

- they are confident that requesting examination will result in the Canadian Intellectual Property Office (CIPO) examining their application;
- they learn the breadth and scope of the claims that CIPO is likely to grant;
- they learn whether their invention is considered patentable by patent offices of the United States and Europe; and
- they learn whether the products covered by their patent application are likely to be commercialized.

Although there may be strategic considerations other than regulatory delays, statistics indicate that applicants for Canadian biotechnology patents request examination of such patent applications at a much lower rate than the average for applicants of other patent classifications (see Section 6.3). Of course, there is no point in requesting examination until applications filed under the old *Patent Act* are dealt with. Nevertheless, the Draft Regulations Respecting the *Patent Act*, which implements the provisions of Bill S-17, should be adopted by CIPO in 1995. According to these regulations, inventors will be allowed only five years to request an examination of their patents. This should help reduce the delay.

The decision to commercialize a product is partially based on a number of IP factors including:

- whether the product is patentable in countries having large markets (the United States, Europe and Japan);
- whether it is a "pioneer" product;
- the scope of IP protection to which the product is entitled;
- whether there are blocking patents in countries having large markets;
- whether licences under such blocking patents are available; and
- whether IP infringement litigation is likely to result from commercialization.

Interviews with representatives of firms involved in agricultural biotechnology products and in bioremediation biotechnology products indicated that these firms seek IP protection at the end of the applied research stage once they know whether they will commercialize the product.

The majority of Canadian biotechnology firms seek IP protection in the United States first and then in Canada (see Section 6.1). This is in contrast to most multinational pharmaceutical and biotechnology firms which file for IP protection first in their home country. Furthermore, past studies indicate that Canadian firms tend to file patent applications in other countries at a lower rate than their foreign counterparts.[107]

Seeking IP protection usually involves counsel from a Canadian or U.S. patent practitioner to determine how to protect products. However, many practitioners commented that they had been contacted by Canadian biotechnology firms only once products were in clinical, field or other product trials. These practitioners were surprised that some Canadian biotechnology firms had not considered obtaining IP protection earlier in the development of their products. Their impression was that U.S. biotechnology firms routinely sought IP protection for their products either at the basic or applied research stage. Such practitioners stated that educating Canadian biotechnology firms on the importance of IP protection would help to ensure that protection was sought early in the product development life cycle.

According to interviews, only a few Canadian biotechnology firms find out if there are blocking patents on a product before they conduct research on that product. In contrast, many Canadian biotechnology firms conduct this assessment only once they have the results of their research and are considering developing the product. The companies that undertake patent searches before conducting research have likely developed a global perspective, either by having adopted an international patent strategy or through strategic alliances with other companies.

Practitioners remarked that firms with a sophisticated IP strategy assess the IP position on the product in the United States, Europe and/or Japan first, and then in Canada. Even when there appears to be a blocking patent in Canada, these firms may still proceed with developing and commercializing the product if there is no blocking patent or prospect of a blocking patent in the United States or Europe. The assessment is usually performed by IP practitioners on the instructions of the Canadian biotechnology firm.

Availability of capital plays an important role in determining when biotechnology firms will seek IP protection and the scope of the protection sought. For small biotechnology firms, interviews indicated that a lack of capital delays and reduces the use of patents to protect innovative research.

It was not possible to obtain "representative" stages and time lines of commercialization for health care products (or, for that matter, for any sectoral products) from our survey respondents. The variability of responses to the questions on these activities, using Gant

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[107] French, D.J. "Foreign Patenting by Canadians." *World Patent Information,* Vol. 9, 1987, p. 10.

charts, suggests that most Canadian biotechnology firms are still at an early stage of commercialization and have not passed through all the stages in the commercialization time line.

Typical commercialization activities for a therapeutic health care biotechnology product (or vaccine product) and typical time lines for those activities are shown in Table 4.3. Product development begins with bench-level, applied research which is assumed to extend over about two years. This stage is followed by animal studies for toxicological and related investigations over two more years. If the evidence from these studies continues to support commercialization, then clinical trials are begun which last another five years or so. With the completion of these trials, a regulatory submission is made which could take up to three years, or more, for approval. Table 4.3 highlights interview findings that IP protection may not be sought early in the commercialization cycle by Canadian biotechnology firms (year two) but may in fact be deferred until virtually the end of this cycle (year nine). This observation reinforces the view that Canadian firms lack experience and counselling about the importance to their business interests of seeking IP protection early.

Health economics (or market research) is a strategic activity which takes place at various points over the commercialization cycle to determine whether or not product development should continue or be aborted. Pharmacoeconomic (or cost-effectiveness) studies are an essential component of all new health care product development in order to obtain rapid market acceptance in Canada and most other developed countries (including the United States). In Table 4.3, pharmacoeconomic studies are shown to take place during the last two years of clinical trials (Phase III) and through the regulatory approval process. Depending on the size and complexity of these randomized controlled clinical trials (RCTs), Phase III studies can run for two or three years. Production financing is seen to begin at around the same time as the clinical trial activity for the simple reason that the product is required in growing (and standardizing) forms and quantities for clinical trial purposes. Usually, manufacturing facilities are expanded in stages as development proceeds toward market entry.

Table 4.3

Representative Time Lines for Therapeutic Biopharmaceutical Product Commercialization Activities

Commercialization Activities	Representative Product Development Time Lines (years)												
	0	1	2	3	4	5	6	7	8	9	10	11	12
Bench research	---------->												
Intellectual property protection			----------||----------							>			
Animal studies			---------->										
Clinical trials					---------->								
Health economics			----------||----------										>
Regulatory approval	---------->												
Pharmacoeconomic studies								----------||----------					>
Production financing					----------||----------								>

The development of diagnostic health care products extends over a much briefer (and less costly) period for the obvious reason that these products are not destined for use inside the human body. Hence, the regulatory hurdles are less stringent and approval times shorter.

No attempt was made to characterize either agricultural or environmental biotechnology product development activities. However, Chapter 3 provides more detail on a typical bioremediation activity.

4.3 Factors Affecting Profitability of the Biotechnology Sector

In this section, we develop quantitative estimates using discounted cash flow scenarios of the most important factors affecting the profitability of commercializing innovative biotechnology products in Canada (and the United States). Several respondents noted that it was premature to use the word profitability in relation to Canadian biotechnology firms since none had as yet achieved that enviable position. These representatives suggested instead the phrase "ability of Canadian biotechnology firms to raise capital."

Interviews with IP practitioners and industry representatives, and a review of recent literature indicated the following.

- Canada's IP protection for biotechnology inventions, in certain instances, acts as a barrier to global commercial prospects for Canadian biotechnology firms and to their ability to raise capital.

- A number of factors adversely affect the ability of Canadian biotechnology firms to raise capital:
  - reductions in the effective patent term for biotechnology products because of excessive regulatory delays;
  - delays at CIPO in prosecuting biotechnology patent applications;
  - uncertainty in the scope of patent protection; and
  - global costs of obtaining patent protection (see Section 6.3).

A firm's product development strategy begins with the choice of a product which will provide "important improvements" that can be translated into commercial success. This choice is usually unique to the company with its particular blend of technological characteristics and human resources and to the product. The selection and identification of the new product also depend on the product's potential life span which is connected directly to the nature of market competition: the pharmaceutical market with patients, doctors, chemists, government regulatory and reimbursement agencies and pharmaceutical companies being the main components.

The evaluation of the product's ability to recover R&D costs must consider:

- the number of market countries;
- relevant legislation pertaining to the product;
- the international regulatory regime;
- the patent situation;
- development costs associated with the pharmaceutical formulation;
- trends in the therapeutic class;
- sales value in countries which are potential producers;
- access to, and control of, the raw material;
- internal production of materials otherwise bought from external suppliers;
- flexibility in the company's plant and equipment usage; and
- ecological disposal considerations.[108]

Barber notes that in pharmaceuticals, there is no meaningful "typical" life cycle.[109] Some products last only a few years. Others, such as aspirin, have already lasted over a hundred years. During the first part of a product life cycle, as sales increase through introduction, acceptance and into the maturity phases, the sales value and volume curves often increase together. As the product reaches maturity and encounters competition, a common reaction of companies is to reduce the price in an effort to stimulate sales, so the volume curve may continue to rise after the sales curve falls. Eventually, obsolescence results in sales volume falling and the product beginning its final decline as a treatment.

Barber uses the significance of patent expiry to distinguish between three types of products. The first, type X, reaches its peak and declines before patent expiry. In these cases, voluntary price cutting is unusual, and volume and sales curves move in tandem. He notes that these short life cycles are more common in Japan and southern European countries. Generally, no firm outside of the originator is interested in a type X product, except perhaps a contract manufacturer.

For the second type of product, type Y, sales peak around the time of patent expiry causing, perhaps, a sales decline due to lower prices related to generic competition. Ten years may be a "normal" life for such a product. Sales volumes may continue to increase after price expiry but with lowered sales revenues. Type Y products offer market niche opportunities for manufacturers other than the originators but, generally, only when the investment is small, and there is a logical reason for moving into the manufacture of generic copies.

The third, type Z, experiences sales and volume increases even after patent expiry. Eventually, falling unit prices lead to a steady state between specialty prices and active ingredient costs. Type Z products represent an opportunity for many companies. For

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[108] Travierso, N. "Pharmaceutical fine chemicals: R&D as a capability of looking into the future." *Chimicaoggi*, November, December, 1993, pp. 21-23.

[109] Barber, M.S. "Future perspectives in the pharmaceutical active substances business." *Chimicaoggi*, January, February, 1992, pp. 33-39.

instance, the opportunity to produce fixed dose combinations, develop new formulations and establish new uses, creates a demand for the bulk product which may not be supplied adequately by the originator. Type Z products include the following characteristics:

- still expanding in volume at patent expiry (e.g., atenolol, ibuprofen);
- widely used and prescribed as well-understood standards (e.g., amoxicillin, naproxen);
- capable of being and readily used in combinations, or specialty proprietary dose forms (e.g., amiloride, diclofenac, hydrochlorthiazide);
- suitable for over-the-counter use, i.e., advertised to the consumer without prescription (e.g., ibuprofen, cinnarizine);
- capable of being synthesized by a variety of routes; and
- capable of easy purification to a common, high standard of purity and specification.[110]

Besides product choice and life cycle factors, for a potential new biopharmaceutical there are additional factors that must be considered such as development costs. Burrill found that these costs have dropped to an average of US$125 million thanks to innovative out-sourcing and financing of American-based biotechnology firms.[111] Others are not nearly so sanguine and refer to the American Pharmaceutical Manufacturers' Association's survey estimates that, on average, it takes US$231 million and 12 years to bring a pharmaceutical product from early-stage research to regulatory approval.[112]

Further complicating analyses of potential profitability of new biotechnology products is the management of risk which does not appear on a company's ledger sheet, but which is an overriding presence in any product development exercise. Risk of failure has been addressed in another section of this report, however, we simply note that its presence and estimation condition the investment climate (viz., expected rates of return) in which product development activity takes place. In terms of risk, a product's potential cost effectiveness is becoming the key measure of its market acceptability and therefore the single most important criterion in investor decisions.

Given these realities, we have constructed a typical rate of return model which conforms roughly to the life cycle dynamics of a cross between the type Y and type Z examples described above. For ease of calculations, we have pegged R&D costs at US$100 million and distributed them uniformly over a 10-year period. These costs were assumed to include all product-specific developmental undertakings except for process development for manufacturing and quality control. These manufacturing costs are contained in the capital

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[110] Ibid

[111] Burrill, G.S. and K.B. Lee, Jr. *Biotech 94: Long-term value, short-term hurdles.* 8th Annual Report on the Biotechnology Industry, Ernst & Young, United States, 1993.

[112] Shamel, R.E. and M. Keough. "Trends in biopharmaceutical product development and commercialization." *Genetic Engineering News*, Vol. 14, No. 1, January 1, 1994, pp. 6-8.

costs for new production facilities ($50 million) constructed in years nine and 10. Some of these costs can be considered R&D costs (which would bring our total R&D costs more in line with the Burrill figure). Also, manufacturing costs could be distributed over years six to 10 to simulate the step-up staging of manufacturing capability. Our example avoids this level of detail without, we hope, affecting the conclusions drawn from the analyses.

Other key assumptions of the rate of return model include:

- a 20-year patent term which means that market entry is expected by the 11th year, implying an "effective" patent term of 10 years;

- the product being eveloped by a global pharmaceutical company, the only enterprise with enough cash reserves to commit on its own to the large outlays, extended time horizons and risks characterizing the development of therapeutic biopharmaceuticals;

- the product being intended for a global market, with the North American continental market being the primary target for sales, followed in turn by Europe, Japan and other Asiatic and world countries;

- capital costs written off using straight line depreciation in the first five years of income generation (years 11 through 15);

- gross income based on annual sales less marketing and distribution expenses;

- sales expenses assumed to amount to 10 percent of selling price [In each simulation, sales were assumed to rise uniformly to a peak level of $X in two years (year 12) and to remain there until year 20 when their level begins to decline (uniformly over the next four years)];

- manufacturing costs initially set at 40 percent of selling price (with a 2 percent decline in unit costs every two years to reflect efficiencies of scale and operation);

- taxes levied at a rate of 44 percent of the difference between gross income and manufacturing costs;

- the provision of investment tax credits, the federal government's incentive mechanism for R&D performers and Ontario's R&D super allowance to model the impact of these incentive programs [These incentives are based on eligible capital and current R&D expenditures,[113] are valued in this simulation exercise at 10 percent of total R&D costs (i.e., $10 million) and

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[113] Murray, K.J. *Strategies to stretch your R&D dollar*. CCH Canadian Limited, North York, Ontario, 1993.

are applied to taxes in the first year of operations (year 11)]; and

- net income derived as the annual income remaining after the application of taxes and incentives.

The evaluative criterion for this exercise was chosen to be the rate of return (ROR), a performance measure which incorporates the effect of the time value of money and inflation. The ROR, sometimes referred to as the internal rate of return, is the interest (or discount rate) at which the present value of a project's future profits equals the present value of the project's investment. If the capital is generated internally (out of past and current profits) then the value of the capital is related to the value of its other possible uses, to the risk of the project and to the strategic importance of the project. The project horizon selected for our analysis was 20 years, the current patent term in Canada. Some readers may prefer higher R&D, capital costs, gross income and production cost figures. The ROR estimates in this analysis, however, remain invariant if all figures are scaled up or down by any factor (e.g., 50 percent).

We also noted that large firms in the health care sector in our survey of the Canadian biotechnology industry (Table 1.9) reported a required ROR on equity of 20.2 percent. We therefore looked for a stream of income which would yield this ROR over a 20-year patent term. Given the assumptions in our simulation exercise, a scenario with a peak annual income of $265 million will achieve this ROR. Table 4.4 shows the Scenario 3 calculations for a health care biotechnology firm generating a peak annual income stream of $300 million ($270 million gross income). Scenario 3 yields an undiscounted total sales revenue over the 20-year patent term of about $2.8 billion.

Table 4.4

Spreadsheet to Determine Rate of Return for a Hypothetical Biopharmaceutical Selling into the Global Economy

Year	R&D Costs[a] ($M)	Capital Costs ($M)	Gross Inc[c] ($M)	Prod'n. Costs[d] ($M)	Taxes[e] ($M)	Net Income ($M)	Cumulative Present Value ($M) at Various Discount Rates		
							15%	20%	25%
1	-10					-10	-8.7	-8.3	-8.0
2	-10					-10	-16.3	-15.3	-14.4
3	-10					-10	-22.8	-21.1	-19.5
4	-10					-10	-28.5	-25.9	-23.6
5	-10					-10	-33.5	-29.9	-26.9
6	-10					-10	-37.8	-33.3	-29.5
7	-10					-10	-41.6	-36.0	-31.6
8	-10					-10	-44.9	-38.4	-33.3
9	-10	-30				-40	-56.2	-46.1	-38.9
10	-10	-20				-30	-63.7	-51.0	-41.9
11		-4[b]	135	60	18.6	56.4	-51.5	-43.4	-37.0
12			270	120	61.6	88.4	-35.0	-33.5	-31.0
13			270	114	64.24	91.76	-20.1	-24.9	-25.9
14			270	114	64.24	91.76	-7.1	-17.7	-21.9
15			270	108	66.88	95.12	4.6	-11.6	-18.5
16			270	108	71.28	90.72	14.3	-6.7	-16.0
17			270	102	73.92	94.08	23.0	-2.4	-13.9
18			270	102	73.92	94.08	30.6	1.1	-12.2
19			270	96	76.56	97.44	37.4	4.2	-10.8
20			202.5	72	57.42	73.08	41.9	6.1	-9.9

Notes:

[a] Includes all development costs (bench R&D, animal studies, clinical trials, IP protection, premarketing, pharmacoeconomic studies, regulatory data packages, etc.) except process development for manufacturing and quality control.

[b] Working capital.

[c] Gross income equals sales less marketing expenses (valued at 10 percent of sales).

[d] Production costs are estimated at 40 percent of sales. Unit cost of production declines by 2 percent every two years.

[e] Taxes are based on 44 percent of gross income less production costs. Year 11 taxes are reduced further by the application of the investment tax credit (rated at 10 percent of all development costs or $10 million). Years 11 through 15 taxes are reduced further by straight line depreciation of capital costs (@ $10 million per year).

We generated seven scenarios and employed Scenario 3 as our base for comparative purposes (Table 4.5). The simulations allowed for the determination of the effect of price, regulatory delays, R&D costs and production costs on the ROR.

- A decrease of 20 percent in price (Scenario 1) yielded a decrease in the ROR of 2.4 percent.
- A one-year regulatory approval delay (Scenario 4) led to a decline in the ROR of 2.8 percent.
- A two-year regulatory approval delay (Scenario 5) led to a corresponding decline of 5.2 percent.

- A 10 percent increase in R&D costs (Scenario 6) led to a modest decline in the ROR of 0.1 percent.

- A 10 percent increase in production costs (Scenario 7) led to a larger decline of 1.1 percent.

Table 4.5

Discounted Cash Flows (in $M) and Rates of Return for Various Illustrative Scenarios

Scenario	20-Year Cash Flows (in $M) for Various Discount Factors					Rate of Return	Impact on ROR
	10%	15%	20%	25%	30%		
1. Sales peak of $250M per year		25.3	-2.9			19.5%	-2.4%
2. Sales peak of $500M per year		108.4	41.8	10.0	-5.3	28.3%	6.4%
3. Sales peak of $300M per year		41.9	6.1	-9.9		21.9%	
4. Scenario 3 with a one-year regulatory delay		24.3	-5.0			19.1%	-2.8%
5. Scenario 3 with a two-year regulatory delay	64.2	7.6	-14.8			16.7%	-5.2%
6. Scenario 3 with a 10% increase in R&D costs			6.1	-10.5		21.8%	-0.1%
7. Scenario 3 with a 10% increase in production costs		34.8	2.3	-12.0		20.8%	-1.1%

Production cost shifts had a larger impact on ROR than did R&D cost shifts because the former affected net income directly. However, because of the much smaller capital outlays of discounted R&D expenditures, R&D costs had a more modest effect on overall cash flow. This latter finding suggested that the impacts of all associated features of new product development (e.g., IP protection, regulatory data package costs and clinical trials) which are buried in R&D costs may be less than previously assumed.

We ranked the impacts of these various factors in terms of their potential effect on a firm's profitability. In order of decreasing negative impact on the hypothetical firm's performance (with the estimated effect on ROR shown in brackets), the factors are:

1. Two-year regulatory approval delay (5.2 percent).

2. One-year regulatory approval delay (2.8 percent).

3. Price decrease of 10 percent (about 1.4 percent).

4. 10 percent increase in production costs (1.1 percent).

5. 10 percent increase in R&D costs (0.1 percent).

- The key finding from the ROR analysis is that the profitability of biotechnology firms is most seriously affected by protracted delays in regulatory approval.

Survey respondents reported a current average review period of 33 months before Canadian regulatory bodies responsible for new product approvals for licensing. If this delay could be reduced to six months, it would improve the ROR on investments by biotechnology (and pharmaceutical) firms by at least 5.5 percent. This would undoubtedly have a major positive influence on the Canadian investment climate for this industry.

4.4 Institutional Arrangements in the Biotechnology Sector

In this section, we review frequently used institutional arrangements which facilitate innovation in the Canadian biotechnology sector and the relationship of IP protection and regulatory approval to these arrangements.

4.4.1 University–Industry Agreements

From the university's perspective, the object of these university–industry agreements is twofold:

- to forge an alliance between the university and industry; and
- to raise funds.

Biotechnology firms forge alliances with universities only if the latter have biotechnology products or processes that are patentable in important markets. This requires the university and its scientists to maintain the confidentiality of biotechnology products or processes until IP protection is in place. To attract industry, universities are attempting to gear their research toward applied research with industrial applications and to assuage the concerns of traditionalists who view the growing reliance of university researchers on private sector funding as compromising academic independence.[114]

Indeed, one government official (and another representative of the Canadian generic drug industry) deplored the fact that it was virtually impossible to obtain independent critical advice on policy development from Canadian academics engaged in biotechnology research because of their growing dependence on financial support from the industry.

Confidentiality is a major obstacle to the commercialization of biotechnology inventions by universities and research institutes. There is an inherent conflict between a scientist's responsibility to publish research (to advance knowledge and gain academic merit or additional funding) and the industry's insistence on confidentiality until domestic and international patent applications have been filed. Even when a university has a technology transfer office or an IP department, interviews indicated that industry must often educate

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[114] Drews, J. "The Changing Research Roles of Industry and Academia." *Scrip Magazine*, 1993, 38; Munsche, P. "Who's to navigate? Who's to steer?" *University of Toronto Bulletin*, Vol. 20, Jan. 31, 1994, p. 20; Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." *Canadian Intellectual Property Review*, Vol. 10, 1993, p. 347.

the scientists on the importance of confidentiality and IP protection. Universities' efforts to educate their own scientists in these areas have met limited success.

Some technology transfer officers indicated that universities require more funding from the federal government to ensure that inventions are properly protected. Because universities are currently not seeking patents for many biotechnology inventions because of the high costs of global patenting. Failure to protect such inventions may harm the future growth of Canadian biotechnology. Since universities cannot afford to protect adequately many inventions, these proprietary technologies are not considered for commercial development by Canadian biotechnology firms (and Canadian and foreign pharmaceutical corporations).

In the United Kingdom, the government has attributed the relative lack of success of U.K. biotechnology firms compared to U.S. biotechnology firms to the lack of an entrepreneurial culture which facilitates the sophisticated technology transfer arrangements between U.S. academics and commerce.[115] During interviews, practitioners remarked that this also seems to be the case in Canada.

4.4.2 Strategic Alliances

Strategic alliances (SA) are usually formed to benefit from the other firm's competitive advantages. The relative size of biotechnology firms to partners entering into strategic alliances often varies. Where companies are comparable in size (and where competing technologies are involved), IP is often the reason for the alliance. In some instances, the SA may be formed to pool either complementary or competing IP rights (on technically equivalent products, or where there is overlapping legal equivalencies). In the case of an SA related to competing IP rights, the SA may seek to avoid litigation between the partners.

In many cases, an alliance is preferable to litigation because litigation is expensive, uncertain, public and consumes the valuable time of management and researchers. Alliances, not litigation, enable both firms involved in the alliance to profit by:

- allowing both firms to enter a market (cross-licence);
- allowing one firm to enter a market while the other firm receives royalties on sales of products in that market (exclusive or non-exclusive licence or distribution agreement);
- allowing both firms to work together to enter one market (joint venture); or
- allowing one firm to enter a market while the other firm is compensated through its sale of IP rights (sale).

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[115] Eglin, R. "Bioscience comes off the shelf and gets down to business." *Management Today*, September 1993, p. 14.

Where biotechnology firms differ in size, valuable technology is often the reason for the alliance. For example, a small biotechnology firm with valuable technology may have a limited ability to secure effective IP protection for that technology. However, a larger partner may be willing to seek a licence for that technology, ensure that the technology is properly protected in major industrialized countries and enforce IP rights by assuming control over any litigation relating to that technology. The larger firm provides capital, access to technology or other compensation to the small biotechnology firm. Where the small biotechnology firm has no prospect of obtaining IP protection for its proprietary technology, the larger multinational is unlikely to be willing to license the technology.

Interviews with practitioners and members of the Canadian biotechnology industry indicated that IP is critical to strategic alliances. One of the first questions a potential partner asks about the technology which is the subject of the alliance: "What is the IP position on the product or process?"

Canadian new biotechnology firms (NBFs) encounter difficulties in forging strategic alliances with multinationals for a number of reasons.

1. Canadian NBFs are dependent on forming alliances to enter markets, such as the United States and Europe, which reduces their bargaining position.

2. Canadian NBFs need alliances to raise capital, either through royalties, lump sums or the credibility created in the eyes of investors in view of the alliance. This also decreases their bargaining position.

3. Multinationals do not treat Canadian NBFs as equal partners. They tend to withhold information on the true reasons for forging the alliance. Afterward, Canadian NBFs can be frustrated by the way in which the multinationals commercialize the biotechnology product or process.

4. Multinationals have more experience in negotiating strategic alliances relating to IP than do small Canadian NBFs.

4.4.3 Investment Capital

This section describes the different methods of raising capital used by Canadian firms.

Private Placements

Capital can be injected into biotechnology firms via a private placement. This typically involves funding provided by a small group of sophisticated investors. Most private placements require a disclosure document known as an offering memorandum which includes detailed information on the scope of the firm's IP rights to its biotechnology products and processes. Weak IP rights have a negative impact on the firm's ability to raise

capital through a private placement.

Initial Public Offering (IPO)

An IPO takes considerable planning and time. Canadian NBFs planning to raise capital in public markets must consider all relevant issues including disclosure requirements and due diligence relating to the technology assessment and IP protection of their products and processes.[116] The disclosure is contained in a prospectus.

For an NBF, a prospectus will always include the firm's research and product goals, the expected timetable to product commercialization, the nature of the firm's technology, the firm's IP rights to that technology including patents, licences in and out, and any possible conflicts relating to such rights. Securities regulators focus particularly on the NBF's IP rights.

Due diligence means that advisors involved in the public offering probe the firm's operations through a detailed review and analysis of documents, discussions with senior management and personnel. These advisors objectively review and analyze all information to be included in the prospectus including technology descriptions and IP rights. Often advisors will seek the opinions of an independent patent counsel on the status and strength of the biotechnology firm's IP rights.[117]

Nevertheless, neither Canadian Securities Commission officials nor investment firm analysts have sufficient resources to fulfil their responsibilities thoroughly. As a result, there is usually an information gap, or what economists refer to as an "undiversifiable" risk, involved in an IPO from a biotechnology firm. Diversifiable risk is risk to an investor's capital which can be spread across his or her portfolio of investments to yield, on average, an expected cash flow that is very predictable. However, an investor cannot eliminate all undiversifiable, or systematic risk through diversification. For example, if prescription drug sales are closely linked to the state of the economy, then returns on investment in pharmaceutical R&D would depend on the state of the economy as a whole, and investors cannot diversify away these economy-wide risks. As a result, the cost of capital for a given investment reflects only the portion of the investment's risk that is undiversifiable. The technical risks of project failure do not affect the required rate of return for an investment, though they do alter the potential cash flow expected from the investment.[118]

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[116] Elvidge, E.R. "Financing Biotechnology Companies." *Canadian Intellectual Property Review*, Vol. 10, September 1993, p. 291.

[117] Ibid

[118] U.S. Office of Technology Assessment. *Pharmaceutical R&D: Costs, risks and rewards*. Washington, DC:OTA. Report No. OTA-H-522, February 1993.

IP protection is important in raising capital through IPOs. Interviews indicated that IP protection must be secured in major markets (United States, Europe and Japan) to maximize the likelihood of raising capital. For prospective investors, IP is a key dimension of the future potential of the biotechnology firm and its ability to raise capital in the public market. Other important dimensions include strong, focused management and an attractive technology assessment of the worth of the underlying technology.

Our literature review indicated that there is a significant difference in investor mentality in North America compared to Japan.[119] North America's focus on short-term profitability and short-term planning is harmful to an industry, such as biotechnology, that is capital and R&D intensive.[120] The orientation toward short-term profit and strong patent protection has resulted in the "patent as product" concept. Under a market system that attaches high monetary value to a patent, resources are often used to secure and enforce patents rather than to develop technology[121] A few interviewees remarked that Canada's patent system enables multinationals to secure and enforce patents without developing technology in Canada. They pointed out that Canada's policies, laws and regulations enable multinationals to adopt such a course of action and impede the development of biotechnology in Canada.

In Europe, particularly in the United Kingdom, Belgium and the Netherlands, governments have tried to develop the domestic biotechnology industry and lower barriers to market entry.[122] The rules of the London Stock Exchange (LSE) provide an example. Under its old rules, biotechnology firms had to show a five-year profit record before being listed. After government urging, the LSE changed its rules so a biotechnology firm in existence for three years with at least two new drugs in clinical trials could seek a listing (even if the firm had no products for commercial sale). This has resulted in more venture capitalists supporting early-development-stage firms. This, in turn, has stimulated more entrepreneurship throughout the biotechnology industry.[123]

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[119] Gibbons, A. "In biotechnology, Japanese yen for American expertise." *Science*, Vol. 258, November 27, 1992, p. 1431

[120] Zahralddin, R. "Note: The Effect of Broads Patent Scope on the Competitiveness of United States Industry." *Delaware Journal of Corporate Law*, Vol. 17, 1992, p. 949.

[121] Ibid

[122] Peat Marwick. *The Biotechnology Industry in the European Community.* April 1993.

[123] Eglin, R. "Bioscience comes off the shelf and gets down to business." *Management Today*, September 1993, p. 14

4.5 Factors Affecting the Rate of Innovation and Commercialization

This section examines the importance of Canadian standards of IP protection and regulation in relation to other factors which affect the rate of innovation and commercialization of new biotechnology products and processes in Canada. It also identifies weaknesses in the Canadian innovation cycle resulting from new standards of IP protection and environmental regulation which would affect the economic performance of Canadian biotechnology firms.

Survey respondents were asked a series of questions to probe the relationship between existing patent legislation and their firm's ability to enter into agreements either with universities, investment capital firms or with other biotechnology firms (through strategic alliances). The probe also examined whether gaining regulatory approval affected these agreements (Table 4.6).

- Most respondents (73 percent) had entered into at least one agreement.
- Fifty-eight percent entered agreements with universities (with research, health care and agricultural firms showing above-industry averages in this respect).
- Thirty-five percent formed strategic alliances with another biotechnology firm (with health care and research firms above the industry average.
- Twenty-one percent entered agreements with investment capital firms (with health care firms well in front of the rest of the industry).
- A surprising finding is that no surveyed Canadian agbio firms had entered into agreements with investment capital firms. (In the absence of capital from investment capital firms, does agbio financing in this country come from private investors, government or multinationals?
- Most firms (70 percent) improved their access to technology and to research facilities (65 percent) through these agreements.
- Most firms (76 percent) indicated that these agreements included references to patent protection. For such firms, existing patent legislation or patent policy (probably the improved pharmaceutical patent protection under Bill C-91) was helpful to the striking of agreements (in 37 percent of the responses) and a hindrance (in 18 percent of responses). The references to patent protection were helpful to 62 percent (and a hindrance to only 12 percent) of health care firms.

Table 4.6

The Perception of Survey Respondents Concerning whether Existing Patent Legislation (or policy) and Regulatory Approval Helped or Hindered Their Firms to Enter into Various Agreements

	Health	Agric.	Env't.	Supp.	Res'ch	Res'ce.	Total
Q.1: Respondents were asked if their firm entered into agreements with any of the following:							
Agreement with university	72%	63%	53%	51%	75%	37%	58%
Agreement with investment capital firm	38%		22%	19%	19%	18%	21%
Alliance with another biotechnology firm	43%	26%	30%	34%	44%	32%	35%
Entered into at least one agreement	83%	69%	76%	66%	86%	59%	73%
Q.2: Respondents who entered into agreements indicated whether their firm's access to any of the following business areas was improved by these agreements:							
Technology	69%	74%	76%	68%	77%	56%	70%
Research facilities	79%	64%	63%	53%	65%	65%	65%
Production facilities	25%	10%	35%	33%	34%	35%	29%
Financing	44%	27%	50%	45%	59%	41%	45%
Q.3: Respondents who entered into agreements were asked if these agreements included references to patent protection:							
Yes	84%	73%	80%	73%	82%	49%	76%
Q.4: Number of respondents who indicated that existing patent legislation or patent policy helped or hindered their firm's ability to enter into these agreements (as a % of respondents whose agreements included references to patent protection):							
Helped	62%	11%	15%	34%	34%	41%	37%
Hindered	12%	34%	26%	10%	18%	43%	18%
Q.5: Number of respondents who indicated that "gaining regulatory approval" was a factor in entering into these agreements (as a % of respondents whose agreements included references to patent protection):							
Yes	50%	26%	29%	40%	32%	14%	37%

A smaller but positive preponderance of responses from supplier and research firms indicated that existing patent legislation helped their firm's ability to enter into an agreement. The view by agbio firms that existing patent legislation hindered their firm's ability to enter into those agreements may relate to their perception that existing plant breeders' rights legislation provides inadequate IP protection. Since environmental and resource firms would only be marginally affected by the improved IP protection, their slightly negative view of the adequacy of IP legislation, particularly by resource firms, cannot be explained.

- Health care firms (50 percent) and supplier firms (40 percent) led the industry average (37 percent) of firms for whom "gaining regulatory approval" was a factor in the creation of agreements containing references to patent protection. Gaining regulatory approval was a less-important factor in establishing agreements for research firms (32 percent), environmental firms (29 percent), agbio firms (26 percent) and resource firms (14 percent).

- The linkage between the regulatory approval factor and patent protection is essential to the ability of health care biotechnology firms (and their suppliers) to strike agreements and is an indicator of their more advanced stage of development (relative to other Canadian biotechnology sectors).

Our survey confirmed the importance of Canadian standards of IP protection in strengthening the ability of health care biotechnology firms to enter into agreements across a number of business areas that affect their rate of innovation and commercialization. However, we may have uncovered some disquietude among agbio firms relative to the inadequacy of plant breeders' rights legislation.

This part of the report assumes the existence of *new* standards of IP protection and identifies weaknesses in the Canadian innovation cycle which affect the economic performance of Canadian biotechnology firms. New standards of IP protection are reflected in Canada's obligations under the North American Free Trade Agreement (NAFTA) and the General Agreement on Tariffs and Trade (GATT).

Article 1709 of NAFTA addresses patents and gives Canada the right to exclude from patentability:

- diagnostic, therapeutic and surgical methods for the treatment of humans or animals;
- plants and animals other than microorganisms; and
- essentially biological processes for the production of plants or animals, other than non-biological and microbiological processes for such production.

Under article 1709, Canada need not issue patents for products covered by patent applications filed before January 1, 1992 where the products relate to naturally occurring substances prepared or produced by, or significantly derived from, microbiological processes and intended for food or medicine. Thus, in the context of NAFTA, Canadian and U.S. standards of IP protection for biotechnology need not be fully harmonized.

4.6 Analysis of Biotechnology R&D in Canada

Past differences in Canadian government spending priorities for the various domains of biotechnology are still evident in today's funding patterns. Table 4.7 shows federal biotechnology expenditures in the mid-1980s (1984-1985) and in the early 1990s (1991-1992). Three federal departments (Energy, Mines and Resources, Environment Canada and Labour Canada) stated that various environmental biotechnology projects (including biomass and bioenergy projects) were their primary focus. An additional three departments (Forestry Canada, Health and Welfare Canada and National Defence) and one agency (International Development Research Centre) showed some activity in this domain.

- Together, less than $4.8 million (or 8.7 percent) of the $55 million spent by the federal government on biotechnology in the mid-1980s went into environmental applications. The investment in environmental biotechnology rose to $9.6 million (or 12.2 percent) of the $160.4 million spent in 1991-1992.

- In terms of total 1991-1992 spending (which measures internal as well as external federal expenditures), $40.3 million (or 15 percent) of the estimated total of $272 million spent related to environmental biotechnology. Not all of these expenditure totals were for R&D work. Some related to regulatory support (in Health and Welfare Canada and Environment Canada) and to significant work in occupational health and safety in the biotechnology field (in Labour Canada).

Environmental biotechnology continues to remain underfunded relative to health and agri-food biotechnology, although the level of its expenditures and its share of total biotech spending has been increasing over the last decade.

Table 4.7

Canadian Government Expenditures for Biotechnology ($K)

	External Expenditures ($K)		Total Spending ($K)[e]
Federal Department/ Agency	**1984-85**	**1991-92**	**1991-92**
Agriculture Canada	$195	$22,612	$57,812
Consumer and Corporate Affairs	401[c]	435	1,035
Energy, Mines and Resources[a]	1,100	2,842	3,742
Environment Canada[a]	1,476	1,626	3,296
Fisheries and Oceans Canada	118	424	1,144
Forestry Canada[b]	721	4,689	10,589
Health and Welfare Canada[b]	233	9,461	21,471
Industry, Science and Technology Canada	2,600	5,095	6,195
International Development Research Centre[b]	808[c]	315	315
Investment Canada	157[c]	160	160
Labour Canada[a]	22[c]	72	102
Medical Research Council	8,217	51,210	51,210
National Defence[b]	430[d]	600	1,100
National Research Council, NRC-BCP and IRAP-BDP	25,933	30,341	84,741
Natural Sciences and Engineering Research Council	12,529	27,129	27,129
Western Economic Diversification Canada	101[c]	3,377	2,007
Total	**$55,041**	**$160,388**	**$272,117**

Notes:

[a] Predominantly or exclusively environmental biotechnology-related expenditures.

[b] Some environmental biotechnology expenditures.

[c] 1989-1990.

[d] 1986-1987.

[e] For each dept/agency, Total Spending = External Expenditures + (Person Years x $100,000).

Source: "Federal Expenditures for Biotechnology: 1989-1992," ISTC, March 1993.

- The U.S. federal government budget planned to spend $83.3 million for environmental biotechnology R&D in 1993. This represents just 2.1 percent of the federal funds it allocates to all biotechnology R&D, as against 42 percent for health and 5.1 percent for agriculture.

- The fiscal year 1994 budget request by the U.S. federal Biotechnology Research Initiative, an umbrella group of 12 U.S. government agencies with program responsibilities for biotechnology, was US$4.3 billion. Total Canadian spending in 1991-1992 was about 4.5 percent of this amount (in converted currency). An equivalent level of commitment would require more than a *twofold increase* in spending by our government. This indicates that Canada does not support biotechnology research as intensively as does the United States.

Table 4.8

Canadian Biotechnology R&D Expenditures ($M) by Firm Classification, Size of Firm and Type of Research: 1989 to 1993

Firm Classification	1989	1990	1991	1992	1993 Basic	1993 Applied	1993 Total	Gth.rate: 1989-93
Health Care	$34.6	$92.7	$143.7	$196.9	$92.7	$245.3	$337.9	77%
Agri-Food	18.6	260.7	258.5	291.6	56.8	317.7	374.5	112%
Environment	10.9	10.0	12.9	20.9	4.3	25.4	29.7	28%
Supplier	21.6	24.6	30.2	42.8	23.3	30.3	53.7	26%
Research	150.6	171.3	173.0	180.8	129.0	53.3	182.3	5%
Resource	12.9	14.1	14.0	13.0	6.0	7.3	13.3	0.8%
Size of Firm								
1-10	$32.6	$276.9	$282.2	$328.3	$67.9	$329.6	$397.4	87%
11-25	11.4	14.1	17.9	26.8	13.8	30.5	44.4	40%
26-100	43.1	81.9	106.4	126.1	55.5	127.4	182.8	44%
101+	162.1	200.4	225.8	264.8	174.9	191.8	366.7	23%
Total	**$249.2**	**$573.4**	**$632.3**	**$745.9**	**$312.0**	**$679.3**	**$991.3**	**41%**

Note: Numbers may not add due to small sample sizes and rounding.

Table 4.8 provides estimates of Canadian biotechnology annual R&D expenditures for the years 1989 to 1993 derived from data provided by survey respondents in early 1994.

- R&D spending has been increasing at a rate of 41 percent per year, far outstripping the industry's aggregate sales growth (24 percent) over this period. As a percentage of aggregate sales, R&D spending grew from 27.7 percent in 1989 to 47.3 percent by 1993.

- The 1991-1992 federal biotechnology external expenditures of $160.4 million (Table 4.7) are partially reflected in the survey data relating to research firms which show R&D spending in 1991 and 1992 at $173 million and $180.8 million respectively. Basic research was 31.5 percent of total R&D spending in 1993.

- The agri-food sector led all other sectors in R&D spending in 1993 at $374.5 million (37.8 percent of total R&D) followed by the health care sector with $337.8 million (34.1 percent) and research firms with $182.3 million (18.4 percent).

- In terms of basic research in 1993, research firms led with $129 million or 41 percent of all basic research in biotechnology. Health care followed with $92.7 million (30 percent) and agri-food with $56.8 million (18 percent). When ranking firms using basic research as a percentage of total R&D spending in 1993, the order was research firms (71 percent), supplier firms (56 percent), resource firms (45 percent), health care (27 percent) and agri-food (15 percent).

- Most R&D spending in 1993 was concentrated in very small firms (40.1 percent) followed by large firms (37 percent). In 1993, average R&D spending per firm was $1.7 million, $0.7 million, $2.5 million and $9.5 million for very small, small, intermediate and large-sized firms respectively.

Table 4.8 data should be considered in the context of total R&D costs for recombinant deoxyribonucleic (rDNA) sectors shown in Table 1.21. That table breaks spending down by end use sector and type of rDNA product (animal, plant or microorganism) over the 1989 to 1993 period.

More comparative statistics on 1993 R&D spending in Canada's pharmaceutical and biotechnology industries are shown in Table 4.9. The data show that Merck Frosst, a U.S. multinational, is the leader in R&D spending, followed by Connaught Laboratories, a former Canadian-owned firm, and Apotex Inc., a Canadian generic drug firm. Novopharm Ltd, another major Canadian generic drug firm, is in 10th place in this list. Among Canadian NBFs, Allelix is in 17th place, followed by Biochem Pharma (18th place), Biomira (20th), Quadra Logic Technologies (21st) and Hemosol (26th place).

Table 4.9 shows that Canadian generic and NBFs are rapidly establishing their presence among Canada's top pharmaceutical and biotechnology R&D spenders.

- In 1993, the multinational pharmaceutical companies accounted for 79.9 percent ($440.6 million) of the total R&D spending of $551.7 million shown in Table 4.9. Note that this is somewhat less than the total 1993 R&D spending of $503.5 million reported by the Patented Medicine Prices Review Board (PMPRB) for 70 reporting companies which are Canadian subsidiaries of foreign multinational pharmaceutical and biotechnology firms.

- Canadian NBFs accounted for $56.6 million (10.3 percent) of total 1993 R&D spending.

- Canadian generic drug firms were responsible for $54.5 million (9.9 percent).

Table 4.9

Canada's Top Pharmaceutical and Biotechnology Firm R&D Spenders and Their Revenues in 1993 ($M)

Company	R&D Spending ($M)			Revenue ($M) in 1993	R&D % of Revenue
	1993	1992	Change (%)		
Merck Frosst Canada Inc.	79.0	75.9	4.1	516.0	15.3
Connaught Lab. Ltd	58.0	44.0	31.8	315.0	18.4
Apotex Inc.	34.5	27.4	25.8	239.0	14.4
Glaxo Canada Ltd	30.0	27.8	8.0	285.0	10.5
Boehringer Ingelheim (Canada) Ltd	28.9	28.1	2.8	73.2	39.4
Marion Merrell Dow (Canada) Inc.	28.7	24.3	18.1	264.9	10.8
Wyeth-Ayerst Canada Inc.	27.8	20.9	32.9		
Ciba-Geigy Canada Ltd	21.9	18.7	17.1	457.7	4.8
Hoffman-LaRoche Ltd	21.2	11.0	92.7	86.0	24.7
Novopharm Ltd	20.0	19.1	4.7	230.0	8.7
Miles Canada Inc.	19.2	13.4	43.3	629.1	3.1
Eli Lilly Canada Inc.	17.2	17.2	0.2	243.5	7.1
Astra Pharma Inc.	16.8	12.8	31.3	178.0	9.4
Ortho-McNeil Inc.	16.3	15.3	6.5	150.0	10.9
MDS Health Group Ltd[a]	14.5	8.4	71.9	639.7	2.3
Sandoz Canada Inc.	13.6	12.0	13.3	164.3	8.3
Allelix Biopharmaceuticals Inc.	13.1	10.1	30.2	7.5	175.7
Biochem Pharma Inc.	12.8	9.6	33.9	36.6	35.1
Warner Lambert Canada Inc.	12.8	13.9	-8.0	350.0	3.7
Biomira Inc.	12.0	13.2	-9.0	4.6	261.1
Quadra Logic Technologies Inc.	11.5	9.4	22.4	1.2	985.7
Burroughs Wellcome Inc	9.2	6.3	46.8	129.4	7.1
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Hoechst Canada Inc.	9.0	7.6	18.6	262.4	3.4
Rhone-Poulenc Rorer Canada Inc.	8.7	6.1	42.6	102.9	8.5
Schering Canada Inc.	7.8	7.1	9.4	124.0	6.3
Hemosol Inc.	7.2	2.4	200.0	1.5	477.6

Note: [a] Classified as a health services company.

Source: Data extracted from the Canadian corporate R&D data base and republished in *Report on Business*, September 1994, pp.85-86.

4.7 Global Trends Affecting Commercialization of Biotechnology

This section explores key global trends affecting the commercialization of health care biotechnology products, especially those affecting the rate of innovation and the time to market, and the regulatory and market barriers facing Canadian health care biotechnology firms internationally.

Several important global trends with repercussions on the Canadian health care biotechnology community stem from the fact that the global pharmaceutical industry is in crisis. The year 1993 marked a watershed in the industry.

- There were U.S. health care reform proposals and sharp sales declines in some European markets owing to budgetary restraints and general pressure on prices in all markets.

- There were layoffs and budget cutbacks in Canada, the United States and Europe by the major multinationals.

- Employment in the total drug industry in Europe fell by 1.4 percent in 1993 to 475,000 after 20 years of increases, and 27,000 jobs could go by 1995, according to the European Commission (EC), the regulation-drafting body of the European Union. Comparable figures for Canada are unavailable.

This consolidation in the international pharmaceutical industry will likely continue, albeit in abated form, over the next decade. Another aspect of change in the pharmaceutical industry is the move to "vertical integration" downstream as drug companies ally themselves with health management organizations (HMOs) in the United States.[124]

Health economic factors (pharmacoeconomics) are becoming as important as therapeutic factors. Regulators, insurers, suppliers, prescribers, interest groups and patients now have influence on products. This vastly increases the complexity of the target audience for pharmaceutical marketers. Under these circumstances, if the aim is to grow faster than the market rate, then share will have to be taken from others. As a consequence, competition, both in a business and a research sense, will become more intense.[125] This phenomenon of mergers and acquisitions in the pharmaceutical industry will probably result in stronger monopolistic powers by the remaining firms, especially in specific therapeutic classes.

R&D will be particularly vulnerable as the pharmaceutical industry restructures. The costs of developing new entities are rising fast as therapeutic targets become harder to achieve and regulations become more complex. The pharmaceutical industry still estimates the R&D costs of bringing a new product to market at between US$250 million and US$350 million. The levels of global sales revenue which need to be generated to achieve acceptable rates of return on investment were shown in Section 4.3.

Some analysts foresee the day in the near future when patients or their surrogates (e.g., formulary or HMO drug managers, interest groups, regulators or insurers) will tell the industry what products they want. As with the auto industry, which has moved from mass production of identical cars to tailored production to suit individual preferences, the pharmaceutical industry will move from blanket treatments based on the risk to the population as a whole to tailored care based on individual patient profiles using, for

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[124] News report: "Transfusing the lifeblood of the industry." *Chemical & Industry*, Vol. 14, July 28, 1994, p. 548; McLachlan, A. and F. Sauer. "What does the future hold for the European pharmaceutical industry?" *Chemical & Industry*, Vol. 12, June 21, 1993, p. 450-453.

[125] News report: "Transfusing the lifeblood of the industry." *Chemical & Industry*, Vol. 14, July 28, 1994, p. 548

example, gene therapy. "Virtual" modelling and testing will replace "real"product development. In the future, a drug may go straight from a screen into a product as failures can be more effectively identified using information technologies.

In the future, health care biotechnology company may consist of a small core of generalists, contracting out R&D where necessary and co-ordinating the input of networks of specialists. Strategic alliances and networking with competitors will become even more common (Table 4.10).

- There were a reported 224 new R&D alliances by the top 26 pharmaceutical companies as compared to 19 in 1990, 50 in 1991, 76 in 1992 and 79 in 1993. Of these, 44 percent were in development, 37 percent in discovery and 20 percent in technology.[126]

Table 4.10

Strategic Alliances by the Top Global Pharmaceutical Companies: 1990-1993

Company	Dev't. Projects (% with partner)	No. of Alliances (1990-1993)	R&D Spending ($M)
Glaxo	80 (30)	19	1,304
Roche	143 (24)	15	1,154
Merck	170 (22)	13	1,057
BMS	167 (25)	7	934
Hoechst	126 (24)	6	881
Pfizer	74 (22)	8	863
Bayer	27 (37)	7	794
Sandoz	93 (38)	21	793
SKB	76 (32)	19	727
J&J	73 (26)	4	643

Source: "News Report: Transfusing the lifeblood of the industry." *Chemical & Industry*, Vol.14, 1994, 14, p. 548.

Strategic alliances are attractive to global pharmaceutical companies because they facilitate rapid entry into a new field, access to top scientists and technologies, risk sharing and blocking of competitors. The most popular fields over the last few year have been adhesion compounds, cytokines, gene therapy, human genome/DNA sequencing technology, high capacity screening, drug delivery technology and developing single compounds. In the future, these collaborations will have to be more focused and more "professionally managed." This may mean that, in the future, good scientists will engage increasingly in contract research. In Canada, this trend is reflected in the establishment of dedicated research institutes such as Toronto's Amgen Institute and Astra AB's new Montreal Pain Control Research Unit. Both investments will extend over at least 10 years and will cost $10 million per year to run.

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126 Ibid

Market and regulatory barriers to foreign pharmaceutical products exist for several reasons. Since the thalidomide issue in the early 1960s, all governments have moved to regulate every aspect of the development process, manufacture and distribution of pharmaceuticals. Through the provision of universal health care, many countries have increased their internal drug market to the greatest extent possible, but the process has created monopsonist purchasers who have defended their interests with a plethora of national (or provincial) drug controls. On top of these regulatory constraints, the pharmaceutical industry has to operate across significantly diverging medical prescribing practices.

Consequently, foreign markets are still characterized by fragmentation despite movements, in Europe for example, to harmonize internal markets. Sellers are required to seek marketing approval in each country which results in a long, complex and expensive regulatory process. Thus, detailed scientific scrutiny by the regulatory authority in each country of each product's data package is necessary to receive approval to market that product in that particular country. These applications lead to delays in approvals, reductions in market exclusivity and increased costs. In pending legislation, the EU intends to establish the principle of mutual recognition which should eliminate most of the delays and costs under the present regime. In addition, manufacturers will be able to acquire a single marketing authorization valid throughout the EU from a central European medicines agency which should allow swifter access to internal markets.[127]

Countries of the European Free Trade Agreement (EFTA) have already accepted the full body of EU pharmaceutical legislation in signing up to the European Economic Area Treaty (EEA), and future co-operation with Central and Eastern Europe will probably evolve along the same lines. Nevertheless, important differences in licensing requirements remain between the EU and two of its main trading partners, the United States and Japan. These are being addressed through a trilateral process known as the International Conference on Harmonization.[128]

However, pricing is still an issue and will remain so for the foreseeable future. National governments argue that the pharmaceutical market is not normal, and that market mechanisms cannot be relied on to establish prices for pharmaceutical products. This is because neither the decision maker (the physician), nor the consumer (the patient) has any interest in the cost effectiveness of the product since drug costs are borne by the health insurer. Furthermore, patients confer monopolies on new products. Consequently, there is little elasticity of demand. Governments approach this problem very differently, and an overabundance of different national cost-control measures now exists in the EU.[129]

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[127] McLachlan, A. and F. Sauer. "What does the future hold for the European pharmaceutical industry?" *Chemical & Industry*, Vol. 12, June 21, 1993, p. 450-453.

[128] Ibid

[129] Ibid

Controls in the EU have led to wide differentials across member countries in the price levels of drugs that are quite unrelated to their relative costs or efficiency of production. Using an EU-wide base of 100 for average drug prices in 1991, the index values varied as follows: Portugal (57.7), France (63.8), Spain (83.7), Greece (85.5), Luxembourg (94.5), Italy (96.1), Belgium (100.5), Germany (110.5), Great Britain (124.6), Ireland (129.8), Netherlands (134.1) and Denmark (143.3). So while price regulations by national governments may not be a barrier to trade, they clearly introduce distortions into the market. In 1993, many EU countries adopted new measures to control drug costs. Germany imposed a 5 percent price cut on pharmaceuticals, Italy a price freeze and the United Kingdom extended its blacklist of products that would not be paid for by the National Health Service. This scenario is also being played out in different ways in Canada (e.g., through formulary delistings), in the United States (e.g., through HMOs) and Japan.[130]

Another interesting effect of price controls in the EU has been the emergence of parallel imports. Independent traders import brand products from a low-price country and undercut the price of the original product in a high-price country. In other words, manufacturers find themselves competing against their own products in their own markets. Profits that would normally accrue to research-based manufacturers go instead to distributors, with health care providers gaining marginal financial benefits. Another consequence has been the inability by manufacturers to rationalize manufacturing capacity to take advantage of a single market. As a consequence, production costs have more than doubled over the last 10 years.[131]

The EU is also preparing to streamline the regulations governing the contained use of genetically engineeered organisms (GEMs) and their deliberate release into the environment by implementing a two-track approach to ease current GEM regulations.[132] This development is discussed in greater detail in Section 5.3 where environmental control measures applying to biotechnology products in Canada are compared to those in the United States, Europe and Japan.

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130 Ibid

131 Ibid

132 Ward, M. "EU plans to streamline GMO regulations. *Bio/Technology*, Vol. 12, September 1994, p. 864.

CHAPTER 5

ENVIRONMENTAL REGULATIONS AND BIOTECHNOLOGY

This chapter focuses on Canadian environmental and industrial biotechnology firms marketing and using microorganisms and products of organisms in applications such as bioremediation, soil inoculants, mineral leaching, energy production, grease control, biochemicals and biopolymers. Discussions were held with Canadian stakeholders (e.g., from industry, federal and provincial government regulatory agencies, environmental law and public health) and with U.S., European and Japanese environmental biotechnology regulators. We also examined scientific literature drawn to our attention by these parties.

Current precautionary measures and the potential for environmental problems are reported in sections 5.2 and 5.3. We also review the various control measures — voluntary and mandatory (i.e., regulatory) — being taken by the international community (United States, Europe and Japan) and compare those measures to Canada's proposed regulatory framework for the biotechnology industry, namely Part III of the proposed New Substances Notification Regulations (NSNRs) under the *Canadian Environmental Protection Act* (CEPA) (see Section 5.4).[133] Section 5.5 reviews existing subsidies and other programs involving biotechnology, administered either by government or the private sector to aid industry in improving its environmental performance.

5.1 Some Definitions and Background

The "industrial" biotechnology industry can be defined by excluding producer firms selling into the health care, agriculture, food and beverage, and environment end use sectors (as well as biotechnology supplier firms). At present, no Canadian industrial biotechnology companies have commercial scale production of fermentation products, with the exception of ethanol producers.[134] Some companies are producing inoculants (for bioremediation purposes) on a small scale.

While downstream users of industrial biotechnology products in Canada undoubtedly number in the hundreds (and are on the increase), as a rule, they don't consider themselves to be in the biotechnology business even though provisions of Canada's proposed biotechnology environmental regulations under CEPA may govern their use of microorganisms as ingredients in the manufacture of, for example, consumer products. A representative list of qualifying Canadian industrial biotechnology firms (under the above

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[133] *Canadian Environmental Protection Act.* (Assented to June 28, 1988). Queen's Printer for Canada. Ottawa, 1989; *Background information on the draft new substances notification regulations for biotechnology products (part III): microorganisms, biopolymers and biochemicals.* Environment Canada, Health and Welfare Canada, October 1992.

[134] Gannon, D.J., Zeneca Bio Products. personal communication, April 11, 1994

definition) is shown in Table 5.1.

CEPA contains provisions for assessing the health and environmental effects of new substances before they are manufactured or imported into Canada. If these substances are suspected of being toxic, controls can be placed on their use. For the purposes of CEPA, the Domestic Substances List (DSL) is the basis for determining whether a substance is new to Canada. It contains all substances known to have been manufactured, imported or in commerce in Canada during the three-year period 1984 to 1986. Substances specified on the DSL are not considered new to Canada and will not require notification under the NSNRs.[135]

Table 5.1

Representative List of Canadian Industrial Biotechnology Firms

Company	Products
Biolix Inc.	Organisms and bioreactors for mineral bioleaching
BV Sorbex Inc.	Metal biosorbents
Coastech Research Inc.	Mineral bioleaching
Enviromine Inc.	Mineral bioleaching
Fluor Daniel Wright Eng.	Mineral bioleaching
Forintek Canada Corp.	Biopreservation of wood
Gemini Biochemical Research Ltd	Products and services for oil recovery and coal mining
Genencor International	Enzymes for pulp and paper, textiles
Iogen Corporation	Enzymes for pulp and paper, textiles
Kelco Canada Inc.	Xanthan gum
Kiseki Technology Inc.	Bioproducts to enhance oil well productivity
Miles Laboratories	Industrial enzymes
Mohawk	Ethanol production
Novo Nordisk Canada Inc.	Enzymes for detergents, textiles, pulp and paper
Pfizer Canada Inc.	Enzymes, gums
Recbiomine Inc.	Gold ore bioleaching
Sandoz-Repligen	Enzymes for pulp and paper
Temeco Enterprises Inc.	Ethanol production
Zeneca Bio Products	Enzymes for pulp and paper

Note: This list of companies and associated products is representative but not necessarily complete.

Source: See Footnote 134.

Biotechnology products which will be subject to regulation under the proposed Part III of the NSNRs are microorganisms, including both naturally occurring microorganisms (NOMs), genetically engineered or modified microorganisms (GEMs) and the direct products of microorganisms and other organisms such as biochemicals and biopolymers that are not regulated under other federal acts.

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[135] "Biotechnology products regulation: provisional list of domestic substances released." *Environmental Policy and Law*, December 1993, p. 308.

A biotechnology component to the DSL is being developed. However, due to the recent evolution of the Canadian biotechnology industry, few products had been commercialized by the 1984 to 1986 time frame. As a consequence, the provisional biotechnology DSL (*Canada Gazette*, Part I, Nov. 20, 1993) contains only one microorganism and nine biochemicals/biopolymers.

From discussions with Environment Canada officials, we learned that the promulgation of the chemical regulations under CEPA on June 30, 1994 meant that two transitional periods were defined (the first running from January 1, 1987 to June 30, 1994 and the second from July 1, 1994 to the date of promulgation of the CEPA biotechnology regulations). Canadian firms whose biotechnology products are subject to CEPA and were in commerce in Canada during that period will receive special consideration. When the CEPA biotechnology regulations are promulgated, such firms will be required to provide notification for these products according to the regulations but will not have to cease importation, manufacture or sale (provided that the notification is deemed satisfactory). Their applications will be considered under schedules of the proposed regulations with less onerous reporting requirements: either Schedule XVII (which applies to indigenous organisms), Schedule XVIII (for contained facilities) or Schedule XIX (for experimental field studies). (Note that schedule numbers quoted here relate to the July 1993 draft regulations and may have been changed.) Their products and corresponding uses will be added to the DSL which, as a consequence, should begin to grow. For example, Canadian firms using commercial and industrial enzymes will fall into this category of notification requirements.

In situ bioremediation, used to clean up contaminated groundwater aquifers and surface soils, can achieve its objectives through the application of appropriate knowledge in microbiology, hydrodynamics and engineering.[136] However, some projects have encountered difficulties for a variety of reasons (e.g., residual concentration of pollutants following treatment remained above targeted guideline levels or project duration extended well beyond planned time frame). Researchers have noted that the science and engineering of bioremediation have not yet progressed to the point of reliably ensuring predictability of performance. Reasons for this situation include:

- the heterogeneity of sites, soil types and treated pollutants;
- a lack of information on the factors governing microorganism activity in the soil (e.g., catabolism of pollutants, bioavailability and measurement of biological activity);
- a lack of quality control on pilot studies and large-scale tests;
- a lack of a methodology for assessing a soil's biotreatability potential; and

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[136] Rittman, B.E., A.J. Valocci et al. *A critical review of in situ bioremediation.* Gas Research Institute, Chicago, August 1992.

- a lack of a methodology for adequate monitoring of the performance of a soil biological treatment system.[137]

An article reviewing the factors affecting survival and the establishment of NOMs and GEMs, and technologies available for detecting, monitoring and containing (and possibly destroying) these microorganisms in the environment, makes the following points:

1. Ecological risks involved in releasing both NOMs and GEMs into the environment can be evaluated based on the potential and expected effects they may have on the ecosystem into which they are introduced. It is important to consider the purpose of introducing the microorganisms as well as the present and proposed future uses of the site.... If the site is to be completely decommissioned, pathogenicity and metabolic waste characterization are critical. Health-related effects must be acceptable or not present and meet regulatory guidelines. Additionally, risks associated with accidental releases of microorganisms require careful considerations.

2. The strain (of released microorganism) must be well characterised. Detection methods such as gene probing and immunological techniques are useful only if the target microorganism is known. The released microorganism must be easily distinguished from the natural microflora if the site is to be suitably monitored. Monitoring the fate, survival and effects of introduced microorganisms is essential for determining ecological effects caused by their release. Also, if released microorganisms have to be contained or rendered non-viable, there must be some known chemical or physical procedure for this purpose. This may be a difficult task to carry out once microorganisms are released into non-contained environments such as lakes and rivers.

3. Microorganisms should be well characterised with respect to pathogenicity and the production of metabolic wastes. In most cases, the microorganism should be non-pathogenic or produce no substances harmful to humans, animals and plants.... The site and purpose of introduction will determine the extent and range of pathogenicity acceptable.

4. Microbial dispersion may also be of some concern. If chemicals are leaching from a waste site into groundwater, streams or lakes, then the potential for released microbial cells to be dispersed may also be significant. Microorganisms may be dispersed from intended locations depending on local weather conditions and hydrogeology. When soil dries at the surface, dispersal of microbes by air (e.g., dust carried by wind) may occur. This may be more significant for microbes that form a resting form like a spore.

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[137] Samson, R., C.W. Greer and J. Hawari. *Demonstration of a new biotreatability protocol to monitor a bioprocess for the treatment of contaminated soils.* Biotechnology Research Institute/National Research Council. December 9, 1992.

Additionally, flies, bees and birds may act as vectors for transport to or from remote locations.

5. Potential ecological effects must also be considered. Released microorganisms may have the potential to upset the ecosystem by out-competing indigenous microorganisms and spreading to other ecosystems.... Assessment of ecological effects may be particularly important if released microorganisms are intended to replace a natural population.

6. A significant ecological effect with respect to introduced microorganisms has not been well defined at this point in time.

7. The method used to introduce microorganisms into the environment may present further ecological risks (e.g., aerosol sprays which inoculate adjacent sites unintentionally).[138]

5.2 Current Environmental Precautionary Practices

This section looks at current environmental precautions being taken by industry and provides a general discussion of industry's standard testing procedures, types of controls and their present costs.

Bioremedial treatment is employed for wastewater, sludge, soil and gaseous emissions. Activities of Canadian companies in these areas range from laboratory research to full-scale commercial operations. In the laboratory, companies generally follow Canadian Medical Research Council (MRC) guidelines which describe safe practices for operating with microorganisms.[139] These control measures probably increase total laboratory costs from 10 percent to 20 percent, but the guidelines also ensure minimal dispersal of organisms and improve the quality and reliability of the research.

Many companies will test novel organisms for pathogenicity early in the development phase (this may cost up to $10,000) and will normally not proceed if the organism is pathogenic. By allowing for a more informed choice, this check can save development money.[140]

For wastewater biotreatment at pilot and full-scale operations, most systems employ a population of organisms built up naturally in the system or seeded from another plant treating similar wastewater (viz., municipal sewage treatment plants). In these cases, no monitoring or controls are employed to control dispersal of microorganisms in aerosols. In

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[138] Jackman, S.C., H. Lee and J.T. Trevors. "Survival, detection and containment of bacteria. Microbial releases. *Springer-Verlag*, Vol. 1, 1992, pp. 125-154.

[139] *Laboratory Biosafety Guidelines*. Office of Biosafety. Laboratory Centre for Disease Control, Health and Welfare Canada, 1990. ISBN 0-662-17695-2.

[140] Gannon, D.J., Zeneca Bio Products. personal communication, April 11, 1994.

municipal plants, these organisms may include human pathogens. In plants that are strictly industrial, pathogens are unlikely. Employees at these plants will normally be advised to be vaccinated against major pathogens, will wear suitable protective clothing and practise very good hygiene. Treated wastewater is normally disinfected (with chlorine or an alternative) before release to receiving waters. Disinfection does add to wastewater treatment costs (increasing overall costs by an estimated 5 percent to 10 percent). In the relatively few cases where a commercial inoculant is employed, no additional monitoring or control measures are generally employed.[141]

For bioremediation of soils and sludges in field trials and full-scale operations, virtually all work has been done with indigenous organisms, either by stimulating *in situ* microbes directly with nutrients or by growing (on or off-site) sample indigenous microorganisms and reinoculating. Normally, the only monitoring is the regular measurement of total microbial counts during remediation. This is useful for both efficacy and environmental issues. Costs are not major in these applications. (According to one estimate,[142] total costs are increased by less than 5 percent; another estimate proposes 10 percent[143]). Workers wear suitable clothing and use respirators if the potential for aerosol exposure arises from the application of inoculants. Other precautions, such as buffer zones from water courses or other sensitive areas, are observed.

The major monitoring and control costs for bioremediation are in measuring the fate of the contaminant(s) during treatment and employing control measures to ensure that leachate, gaseous emissions, and so on, are fully contained. However, these are common features of any remediation process and are not biotechnology controls per se. That is, they do not involve the release of organisms into the environment.[144]

For gaseous emission control, biofilters are becoming more widely used. These generally employ the indigenous population of microorganisms that builds up on the moist filter matrix. Some air sampling may be used to ensure that work place microbial counts are not elevated significantly by the use of biofilters. Again, costs are not major (less than 5 percent).[145]

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141 Ibid

142 Ibid

143 Severn, S.R.T., R. Adams and C.A Hutley. *Bioremediation: strategies to running successful projects*. RZA Agra Inc., Kirkland, WA: February 1993; Severn, S.R.T. and R. Adams. *Treatability studies: a method to reduce the risk of a failed remediation*. RZA Agra Inc., Kirkland, WA: August 1993.

144 Gannon, D.J., Zeneca Bio Products. personal communication, April 11, 1994.

145 Ibid

Environmental precautions are somewhat relaxed for the Canadian bioremediation industry that uses NOMs since the prevalent view is that the environment has seen these organisms already and there is little to be concerned about.[146] Normal precautionary measures include containment (e.g., spraying when there is no wind and providing ample margins between the site of spraying and adjacent streams) and monitoring (e.g., soil bacterial levels and groundwater purity).

Precautionary measures are driven by the type of organism and its level of novelty. Indigenous organisms are placed in one category by the industry and are viewed as requiring less stringent controls. The more novel the organism is, the more containment will be required and the higher will be the associated costs.

GEMs, especially those containing known pathogens, are controlled in the laboratory before field application.

A naturally occurring bacterium for snow making is widely used by ski resorts across Canada. The bacterial surface contains an ice nucleating protein which facilitates and acts as a substrate to reduce supercooling of water and enables it to freeze at higher than normal temperatures. No precautions are taken for this product because the level of environmental risk is either very low or non-existent.[147] When the product was first considered for importation to Canada, the application was reviewed and approved by Environment Canada and Health Canada under the precursor to CEPA, the *Environmental Contaminants Act.*

Most producers of commercial biological remediation products are located off-shore. As a result, the Canadian bioremediation industry is predominantly a user and importer of these products.

Producers license Canadian distributors who may in turn resell to users or be users themselves. It is clearly in the user's interest to minimize the environmental risk arising from use of a biological. So, the choice of products is affected by both the risk and the associated costs. If the choice is between a potential pathogen or a non-pathogen, the latter will invariably be selected. In the absence of a compulsory regulatory regime, the question remains as to how informed the user's choice is with regards to pathogenic risk.

One respondent stated that, when literature and data-base searches reveal that an organism under investigation (or its progeny) is a possible pathogen (either to humans or to the environment), his firm's line of research is immediately stopped because the exposure to general product liability and the possible hazards to workers from proceeding are perceived to be too onerous (or too threatening to the company's public profile).[148] This libel chill has extended to the point where research is curtailed even when the name of the organism

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146 Nestmann, E., Cantox Inc., personal interview, Mississauga, Ontario, January 21, 1994

147 Ibid

148 Jack, T., Novacor Research and Technology Corp., personal interview, Calgary, Alberta, February 17, 1994.

conjures up associations with known diseases (e.g., bacteria with pneumonia-like names). Another respondent speculated whether vaccines could ever have been developed in the current climate of fear.[149]

Our stakeholder discussions identified an issue of liability which has sensitized a portion of the larger research community (in industry and universities) to the point where some strategic decisions are made on the basis of perceived risk rather than perceived opportunity. We made no attempt to quantify or estimate the size or effect of this threat to technology innovation and development, but it reflects an extreme example of "environmental control" conditioned by perceived risk as opposed to scientifically determined risk.

These are local examples of a broad phenomenon affecting biotechnology development everywhere. A recent Organization for Economic Co-operation and Development (OECD) report noted that:

> experts believe that more research is necessary to develop risk assessment in biotechnology, particularly to analyse both the probability and the scale of conjectural accidents in comparison to other technologies...[T]he fact that (expert) discussions began comparatively early has already had three major effects: biotechnology laboratories and industry have been encouraged to choose low-risk microorganisms.[150]

The combination of straightforward compliance with existing occupational and environmental regulations and the presence of liability has induced environmentally responsible behaviour by large industries, known historically as sources of pollution. This behaviour meets or exceeds current environmental regulatory standards. These twin instruments—publicly enforced regulatory standards and court enforced liability costs—can and have already led to environmentally responsible behaviour in certain sectors.

For instance, the chemical industry's Responsible Care program, created by the Canadian Chemical Producers' Association (CCPA), triggers a comprehensive set of actions to meet and exceed standards of occupational and environmental health and safety (and to build credibility for the industry). New products from a company's research program are accompanied by material safety data sheets (MSDSs) which give information on the risks associated with product use. Internal company checks and balances ensure certain levels of performance. These provisions enable, for example, concerned union locals to prompt a company to provide safety information, warning protocols, alarm systems and any additional means necessary to protect workers. This example illustrates how the prods of regulatory legislation (the public instrument) and liability (the instrument available to the private sector) induce responsible behaviour by industries that have been known as

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[149] Mourato, D., Zenon Environmental Inc., personal interview, Burlington, Ontario, February 5, 1994.

[150] Organization for Economic Co-operation and Development. *Biotechnology: economic and wider impacts*. OECD, Paris, 1989.

polluters. The result has been the creation of markets for the application of environmental biotechnology.

A report from the Alberta oil patch notes that smaller independent operators have begun, over the last two or three years, to place waste effluent from their wells directly into barrels for recycling. Before, flare pit sites around oil wells received the products from burned oils (viz., heavy residuals), oil–water mixtures, acidification and dewaxing operations from the front end of the well drilling process. Everything from herbicides to acids, waxes and resins have been found in flare pit sites.[151]

A representative of an Alberta-based environmental biotechnology firm noted that the recent improvement in oil producer behaviour is, in part, the result of a pointed reminder by the provincial government that the estimated costs of cleaning up the oil patch are about $4 billion, or an average of about $50,000 per site. He said that the Alberta government hasn't imposed clean-up requirements on the industry because of the counter threat that operators would simply leave and set up operations south of the border.[152]

A responsible approach to bioremediation of flare pit sites often involves *in situ* remediation using such methods as nutrient stimulation (viz., fertilizers), irrigation to optimize the moisture content of the soil and tilling. In these operations, no exogenous bacteria are added nor are soil samples of the indigenous microbial population removed, cultured and reinoculated into the soil. Bioremediation costs are estimated to run from $35 to $85 per cubic metre of soil depending on the complexity of the underground plume of contamination, the type of soil and the depth of pollutants. The risk of pollutant migration to the level of the groundwater is minimized in many Alberta sites by the presence of heavy clay soils.[153]

The controls exercised by these bioremediation firms include weekly or biweekly sampling to monitor soil levels (and rates of increase or decrease) of hydrocarbon degrading organisms, soil chemistry (to determine whether additional nutrients are necessary) and run-off leachate (to determine if any heavy metals or hydrocarbons are being released from the site). The indexes of performance include the elimination of all "detects" (e.g., benzene, toluene, ethyl-benzene and xylene) and the reduction of polyaromatic hydrocarbon (PAH) levels to standards laid down by the regulations of Alberta's Energy Resources Conservation Board.[154]

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151 McCready, R., Environmental Microbial Services Inc., personal interview, Calgary, Alberta, February 8, 1994.

152 Ibid

153 Ibid

154 Ibid

A respondent added a somber footnote to this story by noting that major oil companies are selling off their low-producing wells to mid-range oil companies to reduce their exposure to liability. In addition, respondents for two Alberta companies in the environmental biotechnology business expressed doubt about whether knowledge of the proposed CEPA biotech regulations will penetrate the communities (and affect the behaviour) of small independent oil operators.[155]

We found additional evidence suggesting no knowledge of the proposed CEPA regulations, not only at the user level, but within the environmental biotechnology industry. The regulations' existence was not known to a mid-sized firm based in Vancouver nor to the head of environmental safety for a large Toronto-based multinational firm, both of which use NOMs for bioremediation.

A respondent described the application of bioleaching in the mining industry and noted some of the cost issues and environmental precautions. The economics of bio-oxidation of refractory sulphide ore that is not amenable to conventional cyanide leaching is driven by world prices for precious commodities. For example, bioleaching gold from low-grade refractory gold ores is viable (given other favourable site-specific factors) when the content of ore piles is about 0.5 ounces per tonne. At US$380 per ounce, bioleaching is economical at under $150 per tonne. The same rule applies to uranium, copper and other mineral extractions using bioleaching. For low-grade refractory gold ores, the technology involves bacterial breakdown of arsenopyrite ore to expose the gold followed by cyaniding for extraction purposes. A major environmental health issue here revolves on the control of acidity in the ore pile to eliminate the production of cyanide gas. This is accomplished by raising the pile's pH level (to around 10) before applying cyanide.[156]

There has been a notable Canadian achievement in the application of biotechnology to *in situ* leaching of uranium at the Elliot Lake sites of Denison Mines in Ontario.[157] Being largely underground, this operation has greatly reduced environmental damage normally associated with uranium mining and surface tailings deposition.

A number of environmental safety issues in mining bioleaching have been noted.[158] For instance, the bacteria used in applications are essentially NOMs, with no record of pathogenesis. GEMs are unlikely to be a priority in current development applications. The dispersal and persistence of the bacteria could be extensive but their activity is only likely to be significant in acidic environments, or those with a potential for acidification

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[155] Jack, T., Novacor Research and Technology Corp., personal interview, Calgary, Alberta, February 17, 1994.; McCready, R., Environmental Microbial Services Inc., personal interview, Calgary, Alberta, February 8, 1994.

[156] McCready, R., Environmental Microbial Services Inc., personal interview, Calgary, Alberta, February 8, 1994.

[157] McCready, R.G.L. and W.D. Gould "Bioleaching of uranium at Denison Mines." In *Biohydrometallurgy.* Edited by J. Salley, R.G.L. McCready and P.L. Wichlacz. Canmet, 1989, pp. 477-485.

[158] Norris, P. *Bacterial mineral leaching: a summary with reference to the application of bacteria.* OECD, Paris, 1993.

(principally some mine wastes and coal spoils) or, for exceptional cases, in hot, acid environments. Gene transfer is very unlikely. However, further work is required to assess its potential. Some techniques for monitoring bacterial species in leaching environments have been developed but require further refinement. The consequences of a large-scale application of biohydrometallurgy could, in some cases, shift the emphasis of potential environmental contamination from air pollution (smelting) to water pollution (acid, metal-bearing leach liquors). Some potential environmentally damaging solid waste would remain for disposal with any mineral processing route.[159]

Biosorption processes (the use of biomass for removing metals from wastewater) have been tested with mine waters as clean-up systems and as potential metal recovery systems, particularly for uranium. Any industrial application would most likely use dead, treated biomass as a "substitute ion-exchange resin." However, some laboratory work has shown that living GEMs could out-perform natural enrichment cultures in mercury removal from wastewater. This area of environmental biotechnology could perhaps more appropriately be considered under bioremediation rather than biomining/biohydrometallurgy.[160]

In its brief existence, the Canadian bioremediation industry has developed a number of proprietary technologies. One example involves an "end-of-pipe" process technology to provide continuous wastewater treatment of industrial effluent before discharge. The technology has been successfully applied in a number of sectors, including the automotive, pulp and paper, and chemical industries, and has been extended to remediate the bilge waters of commercial boats. The equipment is a conventional activated sludge system with the clarifier replaced by a membrane. This eliminates the need for the biomass, or sludge, to settle before discharge since the membrane pores prevent the escape of bacteria. The system requires inoculation with mixed bacterial populations usually obtained from municipal sewage treatment plant sludge.[161]

Performance efficiency is determined by the level of degradation of organics and is measured by biochemical oxygen demand (BOD) or chemical oxygen demand (COD) both before and after treatment. The BOD level is directly related to the concentration of organics in the liquid. Typical intake levels run at about 10,000 mg/litre of either BOD or COD. The product is able to reduce the BOD to non-detectable levels, and the COD to around 1,000 mg/l indicating a 90 percent to 95 percent reduction in organic levels. Depending on the level of organic intake, the cost of treated effluent varies from $0.50 to $5 per cubic metre (or kilolitre).[162]

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159 McCready, R., Environmental Microbial Services Inc., personal interview, Calgary, Alberta, February 8, 1994.

160 Norris, P. *Bacterial mineral leaching: a summary with reference to the application of bacteria.* OECD, Paris, 1993.

161 Mourato, D., Zenon Environmental Inc., personal interview, Burlington, Ontario, February 5, 1994.

162 Malecki, R.A. and B. Blossey. "Biological control of purple loosestrife." *bioscience,* Vol. 43, No. 10, November 1993, pp. 680-686.

Precautions for human health and environmental safety include those normally taken at municipal wastewater treatment facilities. Operators have appropriate vaccinations and wear polymeric suits which allow breathing but prevent exposure to microorganisms. Monitoring equipment and controls ensure that the system operates outside a temperature range within which human pathogens can survive. For this non-genetically modified sludge, controls will either heat or cool the mixture (by adding water) to keep it outside of the critical range.[163]

One respondent[164] outlined the standard operating procedures (SOPs) for his firm, a large American environmental consulting and engineering company performing contract bioremediation predominantly with the petroleum industry, both at the retail level (e.g., gas stations and bulk fuel plants) and non-retail level (e.g., pipelines, trucking company sites and refineries) and with the chemical industry. Most of this work had been conducted in the United States, with some work in Canada.

His firm's SOPs always begin with site characterization and in-house treatability studies to determine whether the indigenous NOMs can actually attack the contaminant under the circumstances likely to be encountered in the field, whether the regulatory clean-up standards are achievable with these organisms and whether there are possible side effects. If there is concern about the possibility of a negative impact (e.g., from an acid or compound produced during the treatment process), the company will go into research mode before proceeding. For example, chlorinated organics have a number of different metabolic pathways that produce side chemicals. The invariant rule is that scientific evidence to support the proposed remedial activity must be demonstrated before the field project begins.

Large and small soil samples are brought to the firm's laboratory for simulation purposes. Because of the patchy distribution of organisms across some sites, a number of systematically gathered samples are necessary for appropriate statistical analysis. The laboratory research determines the achievable theoretical degradating process rates, based on the biochemistry of the organism(s) at the site. Samples are then tested to confirm whether these rates are actually achievable. The data are given to a process engineer who develops a protocol to deliver the required rates. This includes a specific type of growth pattern, depending on whether the project is *in situ* or *ex situ*, and the amounts of required nutrient (and rates of application). Chemical and civil engineers will design the physical system to execute the plan (including, perhaps, aeration pumps, fans, blowers, groundwater removal and reinjection mechanisms). At this point, there is a scientific review to ensure congruence between the engineering design and the proposed remediation objectives. The system is then built and installed.

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[163] Mourato, D., Zenon Environmental Inc., personal interview, Burlington, Ontario, February 5, 1994.

[164] Severn, S.R.T., R. Adams and C.A Hutley. *Bioremediation: strategies to running successful projects.* RZA Agra Inc., Kirkland, WA: February 1993; Severn, S.R.T. and R. Adams. *Treatability studies: a method to reduce the risk of a failed remediation.* RZA Agra Inc., Kirkland, WA: August 1993.

Performance evaluation has two components:

- system performance (Is the equipment operating as it was intended to?); and
- remedial performance (Is the NOM degrading at a rate close to the theoretical maximum?).

The company monitors these performance indicators very closely. Interest in the organism only extends to whether or not it dies off or grows too quickly. In the oil industry, problems arise when the organisms plug pore spaces or die, or when the system goes anaerobic, or its pH lowers, or it produces sulphanated gases (organic gases or simple hydrogen sulphide) which sours the oil.

For small to medium-sized projects (averaging $50,000), this firm's respondent estimated the cost of developing treatability protocols at about $5,000 (or 10 percent). Each protocol covers human health, environmental safety and efficacy issues for each specific project.[165]

Another issue arose during interviews related to "biological containment," i.e., ensuring an organism's perishability in the environment as a containment measure.

The degree of biological containment for any given bioremediation product as a response to environmental regulation (and its associated costs) must be balanced against the price acceptability to the market for bioremediation.

To survive market competition, bioremediation must compete with alternative (and possibly less environmentally favourable) technologies.

In Ontario and elsewhere across the country, firms engaged in soil bioremediation compete with dig and haul operators who remove contaminated soil to landfill sites at a cost that runs upward from $25 per tonne depending on the haulage distance and dumping costs. In Alberta, the competition extends to incineration of the soil at the Alberta Special Waste Treatment Centre in Swan Hills, with reported incineration costs of $1,200 per tonne. The issue of bioremediation's competitiveness is examined later in this chapter with a comparison of proposed Canadian regulations to those of other countries, including the United States.

5.3 Potential for Environmental Problems

Through ignorance or accident, a number of nuisance and even harmful plants, animals and microorganisms have been imported into North America. These problems were not the result of any biotechnology project or activity. Examples include:

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[165] Severn, S.R.T., R. Adams and C.A Hutley. *Bioremediation: strategies to running successful projects.* RZA Agra Inc., Kirkland, WA: February 1993; Severn, S.R.T. and R. Adams. *Treatability studies: a method to reduce the risk of a failed remediation.* RZA Agra Inc., Kirkland, WA: August 1993.; Severn, S., RZA Agra, Inc., personal interview, Kirkland, Washington, February 14, 1994.

- Dutch elm disease, a fungus, introduced through lumber imports or ships which infects North American elm trees;

- purple loosestrife, an imported ornamental plant cleared by the Department of Agriculture which is now invading wetlands and destroying natural habitats;

- milfoil, a lake weed probably brought in by boaters, and now spreading across shallow lakes causing various environmental impacts;

- the kudzu vine, which competes effectively with indigenous plant populations to create erosion control problems in the southern United States;

- the mongoose, introduced into the Caribbean to control rat populations; and

- zebra mussels affecting the Great Lakes.

Table 5.2 provides minimum estimated numbers of non-indigenous species (NIS) in the United States as determined by the Office of Technology Assessment (OTA). At least 4,500 species of foreign origin have established free-living populations in the United States. These include thousands of plant and insect species, and several hundred non-indigenous vertebrate, mollusk, fish and plant pathogen species. According to the OTA report, approximately 2 percent to 8 percent of each group of organisms is non-indigenous to the United States.

Table 5.2

Estimated Numbers of Non-Indigenous Species in the United States[a]

Species with Origins Outside the United States		
Category	**Number**	**Percentage of Total Species in the U.S. in Category**
Plants	> 2,000	
Terrestrial vertebrates	142	≅ 6%
Insects and arachnids	> 2,000	≅ 2%
Fish	70	≅ 8%[b]
Mollusks (non-marine)	91	≅ 4%
Plant pathogens	239	
Total	**4,542**	
Species of U.S. Origin Introduced Beyond Their Natural Ranges		
Category	**Number**	**Percentage of Total Species in the U.S. in Category**
Plants		
Terrestrial vertebrates	51	≅ 2%
Insects and arachnids		
Fish	57	≅ 17%[b]
Mollusks (non-marine)		
Plant pathogens		

Notes:

[a] Numbers should be considered minimum estimates. Experts believe many more undetected NIS are established in the United States. Where number or proportion is unknown, the space has been left blank.

[b] Percentage for fish is the calculated average percentage for several regions. Percentages for all other categories are calculated as the percent of the total U.S. flora or fauna in that category.

Source: *Harmful Non-Indigenous Species in the United States.* U.S. Office of Technology Assessment, Report No. OTA-F-566, September 1993.

- The number and impact of harmful NIS are chronically underestimated, especially for species that do not damage agriculture, industry or human health. Harmful NIS cost millions to perhaps billions of dollars annually. From 1906 to 1991, the OTA report showed that just 79 NIS caused documented losses of $97 billion in harmful effects (Table 5.3). The OTA's worst-case scenario for 15 potential high-impact NIS adds up to another $134 billion in future economic losses (Table 5.4).

Table 5.3

Estimated Cumulative Losses to the United States from Selected Harmful Non-Indigenous Species: 1906 to 1991

Category	Species Analyzed (number)	Cumulative Loss Estimates (1991 $M)	Species Not Analyzed[a] (number)
Plants[b]	15	603	
Terrestrial vertebrates	6	225	> 39
Insects	43	92,658	> 330
Fish	3	467	> 30
Aquatic invertebrates	3	1,207	> 35
Plant pathogens	5	867	> 44
Other	4	917	
Total	**79**	**96,944**	**> 478**

Notes:

[a] Based on estimated numbers of known harmful species per category.

[b] Excludes most agricultural weeds.

Source: *Harmful Non-Indigenous Species in the United States.* U.S. Office of Technology Assessment, Report No. OTA-F-566, September 1993.

Table 5.4

Worst-Case Scenarios: Potential Economic Losses from 15 Selected Non-Indigenous Species in the U.S.

Group	Species Studied	Cumulative Loss Estimates (1991 $M)
Plants	Melaleuca, purple loosestrife, witchweed	4,588
Insects	African honey bee, Asian gypsy moth, boll weevil, Mediterranean fruit fly, nun moth, spruce bark beetles	73,739
Aquatic invertebrates	Zebra mussel	3,372
Plant pathogens	Annosus root disease, larch canker, soybean rust fungus	16,924
Others	Foot-and-mouth disease, pine wood nematodes	25,617
Total	**15 species**	**$134,240**

Note: Estimates are net present values of economic loss projections obtained from various studies and reports on selected potentially harmful NIS. Many of the economic projections are not weighted by the probability that the invasions would actually occur. Thus, the figures represent worst case scenarios. The periods of the projections range from one to 50 years.

Source: *Harmful Non-Indigenous Species in the United States.* U.S. Office of Technology Assessment, Report No. OTA-F-566, September 1993.

The federal government has been engaged in a deliberate release program involving insects as control agents to combat the spread of purple loosestrife throughout Canadian wetland habitats.[166] The program is larger in scope than any contemplated by environmental biotechnology firms. It is interesting to note that it suffers from the same problem that afflicts many environmental bioremediation applications: the inability to demonstrate laboratory efficacy in the field. Several different insect varieties have been released since the program began. None have had any remarkable success in controlling the purple loosestrife.

While there is always the theoretical potential for an environmental problem, in reality there is an existing history of responsible international development of active biotechnology products. In the laboratory, worker health and environmental safety are ensured through adherence with Medical Research Council (MRC) safety guidelines in Canada (corresponding to National Institutes of Health guidelines for the United States) or with good manufacturing practices which, although addressing product quality, add to safety through their stipulations on clear procedures, proper equipment and well-trained staff. There are clearly articulated guidelines in most industrialized countries governing contained and semi-contained laboratory and industrial use of microorganisms in biotechnology.[167]

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[166] Malecki, R.A. and B. Blossey. "Biological control of purple loosestrife." *bioscience*, Vol. 43, No. 10, November 1993, pp. 680-686.

[167] Collins, CH "Safety in industrial microbiology and biotechnology: UK and European classifications of microorganisms and laboratories." *Trends in Biotechnology*, Vol. 8, December 1990, pp. 345-348.

There is a clear need to extend regulatory regimes to control the open release of microorganisms into the environment.

These regulations will keep the pressure on the environmental biotechnology community which is now regulated in an ad hoc manner. They will also conform to developing international standards which will assist Canada's export markets (since linkages between export products and environmentally friendly technologies are becoming a trade issue).

As previously mentioned, producers often build containment aspects into their products, a technique referred to as "biological containment." It has both push and pull aspects since ensuring an organism does not survive in the environment also means that users of bioremediation products, for example, have to keep purchasing supplies to obtain effective biodegradating performance. Complaints have emerged from the pulp and paper industry that the failure of purchased organisms to survive in their holding ponds (for plant effluents) has meant that their remediation costs continually increase per unit of treated effluent. This is another example of product safety, i.e., biological containment, being traded off against product efficacy. The safer the product, the less efficacious it is.

In an ad hoc survey of government, industry and public representatives of the environmental biotechnology stakeholder community, no evidence was found of any human or environmental harm arising from the Canadian environmental biotechnology industry.

Nevertheless, this statement must be tempered by recent anecdotal reports suggesting, for instance, health problems among segments of the labour force not covered by occupational health and safety legislation (e.g., allergies and skin reactions among farm workers from the use of insecticides). While the reports do not refer to the environmental or industrial biotechnology sectors, the potential exists for such problems to arise from exposure to biochemicals and biopolymers.

Several examples follow to illustrate the potential for environmental problems which exist within the environmental biotechnology industry.

Example No. 1

This example from a provincial regulator was repeated in different forms by others. It illustrates an existing potential for environmental problems in certain bioremediation applications. The problem arises because microorganisms used for bioremediation are poorly characterized, and the current Canadian regulatory system to assess their potential for pathogenicity is somewhat ad hoc.

A firm obtained exclusive marketing rights to product X and has applied it at a number of sites. The firm lacks microbiological expertise and accepts, in the absence of convincing scientific evidence, the efficacy claims made by the parent company. Provincial regulators cannot obtain the requisite information to determine product or process safety and efficacy.

The company approached the ministry with a proposal to bioremediate a small amount of soil contaminated with approximately 500 ppm of polychlorinated biphenyls (PCBs). Bioremediation was to involve the addition of a bioremediation product obtained from Europe. The project was to be a demonstration test for the product in support of an application for blanket approval for the process in Ontario.

The product was apparently a consortia of microorganisms which were not identified. While assurances were given by the proponent that the microorganisms were non-pathogenic, data to substantiate these assurances were unavailable. The proponent was asked to obtain approval for importation and use of the consortia from Environment Canada.

While the original product was developed to metabolize petroleum hydrocarbons, and limited cases studies were provided to demonstrate this, the proposed application was for PCBs. Information on the effectiveness of the process toward PCBs was not available.

Site characterization was very limited, the proponent had not undertaken feasibility or treatability studies and had no information on the potential of forming metabolic by-products as a result of the microbial activity on PCBs.

As a postscript, an informed customer would never accept the claims of this bioremediation company without sound scientific evidence that its product really works for PCBs. The respondent noted further that:

> many proponents of bioremediation underestimate its complexity and, as a result, fail to take into consideration site specific factors which can limit its effectiveness and often fail to consider issues such as the formation of potentially toxic intermediates of the bioremediation process. This is a generic problem of the bioremediation industry and should resolve itself as the level of knowledge about the process increases.[168]

The key factor which separates this example from the more responsible behaviour shown by bioremediation firms in the previous section of this report is the absence of microbiological expertise on the project team.

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[168] Bailey, S., Ontario Ministry of Environment and Energy, personal communication, February 7, 1994.

Example No. 2

The above example illustrates a problem potential. Two reports from the Alberta oil patch confirm how this situation can lead to a real problem, not involving environmental safety, but increased production costs. As with the previous example, the presence of microbiological expertise in this second example would have made all the difference in the world.

A company established a business to market an organism developed in the United States to dewax oil wells. The bacteria produce surfactants which are augmented by chemicals. The product is sold with a biological label on it.

The company set up an extensive network of distributors who indiscriminately used the product in applications, some of which failed. The failures involved production problems — souring of underground oil formations or clogging the producing zone in oil wells. One report also noted that the product failed to survive competition with indigenous organisms when it was applied to remediate the soil in certain flare pit sites.

In its defence, the product has had some successes (e.g., in cleaning sludge from tanks and in keeping Utah oil fields operating). However, the failed applications created an unfriendly climate, for the Alberta bioremediation industry, among some oil operators.

Example No. 3

The following example illustrates a potential environmental problem concerning the progenitor organisms used to derive biopolymeric products. Where such organisms possess pathogenic characteristics, their presence, even in minute quantities in the final product, could threaten human health or environmental safety. At the time (in the 1980s), the company in question chose not to take the biopolymers into the market. The company was concerned about the implicit cost associated with the uncertainty surrounding product liability. This example also illustrates the dynamics of market regulation of environmental safety.

During the 1980s, a large Canadian company conducted biotechnology research to develop proprietary, soluble biopolymers from methanol through fermentation processes. The company chose to develop competitor biopolymers to xanthan gum using fermentation means. It developed a number of different polymers (using xanthan gum to provide minimum criteria) from different organisms all of which were able to grow and make their biopolymeric product with a 7 percent methanol solution. All derived biopolymers outperformed xanthan gum.

Were there any NOMs left in the final biopolymers? The company reasoned by analogy as follows. Xanthan gum is derived from a set of organisms called xanthamonads which are plant pathogens. Extra precautions are needed during the gum's manufacture to ensure that no living organisms remain in the final product. Since xanthan gum is an ingredient in food stuffs (e.g., ice creams), health and safety standards are very stringent, and all residual organisms in the final product have to be killed in the factory. This has resulted in extraordinary development and manufacturing costs which are still reflected today in xanthan gum's price despite its sales in the United States in the hundreds of millions of dollars. By analogy, the organisms generating the new, derived biopolymers might also possess similar (or possibly other) pathogenic properties. As a consequence, the company chose not to go into commercial production but was content to develop patents for the technologies.

Our examples suggest several conclusions.

- Microbiological expertise in an environmental biotechnology firm's project team is essential to the final success in any bioremediation undertaking, as measured in terms of health, environmental safety and efficacy.

- An informed user of environmental biotechnology goods and services is still the best guarantee of a salutary outcome. Conversely, uninformed use of these products and services is creating market resistance to environmental biotechnologies in some portions of the country.

- Alternative, environmentally less-favourable approaches (e.g., dig and haul) continue to underprice bioremediation technologies, a situation still not adequately addressed by environmental legislation.

- Lack of public acceptance of biotechnology in general and fear of liability on the part of the industry have dampened scientific endeavour and development in this field.

5.4 Environmental Regulations in the United States, Europe and Japan

It serves the public's interests to protect human health and the environment by regulating the commercial products of Canadian environmental and industrial biotechnology firms. It should be recognized, however, that many of these products will inevitably be used in low volumes by comparatively small Canadian companies. These companies will be vulnerable to cost burdens associated with onerous environmental notification requirements for assessments of their applications for approval to use biotechnology products. Countries around the world are searching for the appropriate level of regulatory control to meet requisite safety standards without stifling technology innovation and commercial opportunities. This section reviews current developments among Canada's global trading partners and compares the various regulatory approaches.

The following material was derived from discussions with Canadian stakeholders (from industry, government and the interested public) and from international regulators (in the United States, Europe and Japan).

During 1993, the OECD conducted a project to develop guidance for regulators in member countries for the assessment of "industrial products of modern biotechnology intended for introduction into the environment," either for testing or for marketing. The primary objectives were to develop guidelines to assess data which would appear in a notification requirement, as well as testing methods to collect that data.

The project focused on biotechnology products which were neither pharmaceuticals, nor pesticides, fertilizers nor foods, but were living organisms intended for use in industrial activities, such as bioremediation, bioleaching and biomining, or for other environmental purposes.

A questionnaire was circulated to member countries in January 1993 to identify whether a regulatory oversight/notification system existed for the types of products described above. If it did exist, what were the salient details, particularly the specific information requirements for the evaluation of the noted products?

A subsequent workshop in May 1993 examined the feasibility of developing a consensus approach to this work and concluded that there was commonality in the national approaches in terms of the data elements forming the notification requirements for these products. It was also recognized that these elements could be categorized according to whether they were obtained from some test method, from descriptive information, from a literature search or from field trial data.

The workshop concluded that future work leading to the exchange of information and data, or even the mutual acceptance of data, was feasible. Such an exercise would be a significant first step in developing guidelines for regulators. The workshop suggested the OECD Secretariat start work on a more detailed comparative analysis to identify specific areas of commonality among national notification/oversight procedures and the data elements in common among these procedures.

Through a compilation of information received on the regulatory oversight systems from member countries [Australia, Austria, Canada, Denmark, Germany, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, United Kingdom, United States and the European Union (EU)], it becomes clear that most participating countries have in place, or are in the process of implementing, a regulatory system. Among the EU countries, the systems are designed to implement European Commission (EC) Directive 90/220 which governs the deliberate release of GEMs to the environment.[169] Among the countries of the European Economic Area, the systems are primarily designed to conform to these same directives, sometimes as a minimum requirement.

When narrowly defined, regulatory systems in comparison countries were solely concerned with living organisms. However, responses from Australia, the Netherlands, Norway and the United Kingdom implied that products of living organisms would fall under broader oversight procedures designed, for example, to assess novel substances. U.S. oversight procedures included living organisms in a special category of regulations originally implemented for the control of novel substances. At one extreme, Canada's draft regulations included both living organisms and their products in one set of common regulations. At the other extreme, Sweden had not, as yet, envisaged control legislation for organism products.

Most participating countries, with the exception of the United States, indicated that industrial products consisting of, or containing GEMs, are, or would be, included in a wider scope of notification and oversight systems for all GEMs. Such products would come under the *Toxic Substances Control Act* (TSCA). At present, a specific set of guidelines under the TSCA are used for GEMs.

Where notification procedures are already in place, there is some variation in the guidelines provided for particular classes of GEMs, including bioremediation agents. For instance, the guidelines issued by the Australian Genetic Manipulation Advisory Committee contain a sub-section explicitly concerned with agents for bioremediation. The draft Canadian NSNRs for biotechnology cover a broader range of products than other member countries (NOMs as well as GEMs) and also include biochemicals and biopolymers. On the other hand, U.S. chemical regulations cover biochemicals and biopolymers.

For most countries, the responsibility for regulatory oversight of these products resides in an environment ministry. In Germany, the Ministry of Health holds primary responsibility. Canada is the only jurisdiction in which responsibility is shared between two departments, Environment Canada and Health Canada. A memorandum of understanding underpins the relationship between all involved ministries in the United Kingdom; a similar arrangement exists among responsible agencies in the United States. Member countries with federal or devolved administrative structures (e.g.,provincial, state or other subdivisions) also pointed out that formal relationships between the central responsible authorities and their regional

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[169] Commission of the European Communities. *Handbook for the implementation of Directive 90/220/EEC on the deliberate release of genetically modified organisms to the environment.* Vol. 1. Brussels, Belgium: Directorate General XI, Environment, Nuclear Safety and Civil Protection, May 1992.

counterparts were part of the process.

Little detail was available concerning administrative practice. Expert committees are used to advise on applications made under guidelines in Australia, New Zealand and the United States. However, the way in which authorities used such advice to implement their statutory obligations was not clear. There seemed to be agreement that a notification/oversight system should be based on a dialogue between the responsible authority and the applicant.

There was a consensus among responding countries that data are required for the biological and safety characteristics of the product, but no clear preference emerged on whether data should also be required for efficacy and/or comparison with existing or alternative processes. In the United States, efficacy is not assessed under the TSCA, but may have to be demonstrated under other regulations for specific applications (e.g., bioremediation processes for PCBs). A recent discussion with an Environmental Protection Agency (EPA) representative revealed that the agency had received its first submission for a GEM for PCB remediation.

Both Norway and Germany require applicants to provide information on possible benefits to the community and compatibility with sustainable development.

Industry stakeholders expressed broad concerns about the cost of the regulatory data package required to fulfil the notification requirements pursuant to the environmental regulation of a specific biotechnology product.

As to the costs from possible time delays of regulatory review, government officials noted that, under the proposed CEPA NSNRs, the longest assessment period is 120 days, with no option to extend the time if the applicant's package is complete. If the assessment uncovers the potential for toxicity, additional notification requirements may be imposed.

One EC spokesperson expressed his personal view when he commented that notification requirements should be central, risk based, product based and specific to the environment in which they will be released. He also said that high-risk applications should receive top priority in the review process. To ensure "one stop shopping," he suggested that bioremediation applications be reviewed by bioremediation specialists, and not by environmental generalists. More specifically, they should be reviewed by specialists in the applicant's product area. This would remove any possible time delay issue in his opinion.

He also noted that there is no legislation specific to bioremediation (i.e., the use of microorganisms to clean up the environment). The EC has regulations for GEMs. The GEM legislation differs from the Canadian approach which looks at biotechnology products. He believes that the Canadian approach of looking at NOMs as well as GEMs makes sense because GEMs should not be singled out by special legislation. By combining NOMs and GEMs in one regulation, the Canadian approach correctly bases its rules on the properties

of the specific organisms used, and not on their mode of origin.[170]

The EC representative noted that the Commission is moving away from the implications in Directive 90/220 on socio-economic impacts. In the future, evaluations of a novel GEM will be based more on the criteria of safety, quality and efficacy, which include the impact on nature and environmental safety, than on the horizontal criterion of environmental and worker protection. This last criterion, sometimes called "the fourth hurdle," has been the vehicle for introducing broader socio-economic issues into the policy debate. Instead, the Commission will normally follow scientific advice.[171] No other country has adopted a regulatory regime for biotechnology products based on criteria other than scientific ones.[172] This view is supported by a recent article which states that changes are under way, in the EC, to the directive on the deliberate release of GEMs into the environment.[173]

While there is no explicit reference in legislation or regulation to a fourth hurdle in Canada, the same result came about when a House of Commons committee recently urged the Cabinet to defer approval for sale of bovine somatotropin (BST) (recombinant bovine growth hormone) for one year to allow more study.[174] BST is an imported agbio product and a direct competitor to bull semen, a Canadian "traditional biotechnology" product marketed by Semex which is yielding growing export dollars for Canada's balance of trade. Both products achieve the same goal, the recombinant deoxyribonucleic acid (rDNA) version through periodic stimulation of a cow's lactation, the traditional version by producing dairy herds with more naturally derived BST.

In closing this discussion on the evolution of the European regulatory environment, it should be noted that there is considerable conflict between the Commission's approach of relaxing biotechnology regulation (and of extending intellectual property protection) and the direction the European Parliament (EP) wishes to take. On February 28, 1995, the EP rejected a compromise draft directive to provide harmonized legal protection for biotechnological inventions. The directive had been under development since 1988. The legal vacuum concerning many intellectual property (and regulatory) issues in

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[170] Davis, B.D. (ed.) *The genetic revolution: scientific prospects and public perceptions.* Baltimore: The Johns Hopkins University Press, 1991.

[171] Commission of the European Communities. *Promoting the competitive environment for the industrial activities based on biotechnology within the community.* Commission communication to Parliament and the Council. Brussels, Belgium. April 19, 1991.

[172] Lex, M., European Commission, Directorate General XII, Science Research and Development, personal interview, February 11, 1994.

[173] Ward, M. "EU plans to streamline GMO regulations." *Bio/Technology*, Vol. 12, September 1993, p. 864.

[174] Chamberlain, A. Canada delays sale of disputed bovine hormone." *Toronto Star*, August 18, 1994, p. C

biotechnology continues.[175]

As various directives come into effect through legislation enacted by member states, a more detailed analysis of individual state's legislation would be necessary to provide a complete picture of the situation in the EU.

In Canada, some 20 or so federal acts were identified by one Canadian regulator as not meeting the standards of human health and environmental safety set by the proposed CEPA legislation (the only exception apparently being the *Pest Control Products Act*). Short of reducing the level of protection to be provided by CEPA, which he indicated that the public would find unacceptable, the only effective course to avoid multiple notification requirements by biotechnology companies would be to amend all deficient acts with an omnibus bill. This should be accomplished before a biotechnology regulation under CEPA is promulgated. Recently, the Department of Justice Canada issued a directive requiring all affected federal departments to rewrite regulations for the acts under their administration to conform to the standards set by the proposed CEPA legislation.

A spokesperson for a multinational in the agbio business noted that biochemicals and biopolymers will be affected by the proposed Canadian regulations. In his opinion, this will jeopardize certain Canadian manufacturing activities, but will not affect imports except, of course, in their country of origin. He gave the hypothetical example of a possible import prohibition of a novel car paint (because of CEPA notification requirements) which might jeopardize automobile manufacturing in Oshawa. However, the regulation would permit the importation of a finished automobile with the same applied paint. He referred to this example as a "finished product exemption" for biologicals. He suggested that diagnostic kits would fall into the same category in the health care sector.

He emphasized that the incremental costs of meeting regulatory requirements in Canada should not exceed the cost incurred for corresponding approvals in larger markets (viz., the U.S. market). The greater these costs are, the more inhibitions he believes there will be for international companies to pursue regulatory approvals in Canada. He cited estimated costs of preparing a U.S. chemical notification package as about $100,000 (cost estimate is from the regulatory impact analysis statement) versus an estimated Canadian cost of $180,000 for the same package. While some would argue that the costs were roughly comparable, he denominated costs in relation to the cost of the U.S. data package. If it is $100,000, then he believes the additional cost to his company to prepare a Canadian data package should be only $10,000 (based on the fact that the Canadian market is about 10 percent of the size of the U.S. market). In this way, his company could achieve approvals in North America for $110,000 and remain competitive. This may be possible if the concept of mutually acceptable data, discussed above, is accepted. It may also be possible to use most of the content of U.S. regulatory data to keep the incremental cost of the Canadian application within bounds.

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[175] Betts, M.T. *Memorandum on EU Biotech Patenting - EurParl Rejects.* Mission of Canada to the European Union, Brussels, Belgium, March 2, 1995.

To reduce costs to his firm, this individual argued for a system of waivers to provide exemptions in situations meeting specified conditions. These waivers would require public acceptance since they are published in the *Canada Gazette* for public comment. The public might argue that the waivers shouldn't apply since they introduce inconsistency into the application of the regulations. He stated that biotechnology companies have an inherent need to retain confidentiality in relation to their product which must be balanced against the public's right to know and its confidence in, and acceptance of, the technology. The proposed CEPA regulations provide for waivers.

He placed his company's strategic planning decisions in the context of cost minimization to retain product competitiveness. In budgeting programs, companies plan on the basis of the official cost of the regulations, and not on the possibility of obtaining allowances or waivers. International companies pursue this logic in determining whether or not a given product should be developed in Canada. He emphasized that CEPA regulators must specify the time requirements and data package costs for Canada in relation to those for the United States and the United Kingdom. He felt they should show where the requirements were greater or less so companies, such as his own, could determine the differences in requirements and the likely outcome of their applications. In this way, companies could decide whether Canada would be an attractive place to develop and commercialize their products.[176]

Most respondents noted that Canada stands alone among world countries in regulating NOMs in addition to GEMs. Two industry respondents noted that municipal sewage treatment plants (STPs) have run satisfactorily, without major environmental impacts, in industrialized countries since the 19th century.[177] Further, the concentration of organisms in their semi-contained or open tanks is enormous (on the order of one mole or about 10^{20} to 10^{21} organisms per tank). These microbial populations are both mixed and indigenous, and the populations change all the time, so it would be impossible to characterize them as required under CEPA.[178] Sewage treatment plant operators are not required to notify under CEPA if they do not manufacture or import a microorganism that is considered new. Environment Canada is developing a code of practice for sewage treatment plants. The question then shifts to industrial operators who use municipal sludge in continuous wastewater treatment systems. Will they also be exempted?

In contrast to these industry viewpoints, recent evidence suggests that problems have arisen from the routine operation of STPs. For instance, the U.S. EPA is discussing whether to act quickly to reduce the risk posed by *Cryptosporidium* in drinking water. This microbial pathogen is spread via farm run-off, municipal sewage wastes and wild animal feces. Currently, the microbe is not covered under the surface water treatment rule of the U.S. *Safe Drinking Water Act*, but the 1993 outbreak in Milwaukee, which affected an estimated

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176 Wearing, J., Monsanto Canada Inc., personal interview, Mississauga, Ontario, February 9, 1994

177 Mourato, D., Zenon Environmental Inc., personal interview, Burlington, Ontario, February 5, 1994

178 Parsons, R., Wardrop Engineering Ind., personal interview, Mississauga, Ontario, January 28, 1994

400,000 people, has put pressure on the EPA and water suppliers to act. Surveys of cattle show high rates of infection. Moreover, the microorganism appears to be fairly widespread in raw surface waters. In addition, *Cryptosporidium* can survive for months in soil under certain conditions. Standard chemical disinfection, such as chlorination, is ineffective against *Cryptosporidium*. Ozonation has been reported to show some promise, but no effective remedy has yet been found.[179]

Because it is still uncertain whether tougher measures will prevent future outbreaks, there is great concern about what to do if *Cryptosporidium* or any other pathogen is detected or suspected of being in drinking water. *Cryptosporidium* has been implicated in at least five outbreaks of gastroenteritis in the United States and as many as seven in the United Kingdom since 1983. In the Milwaukee outbreak, individuals with weakened immune systems (e.g., AIDS patients) suffered the most from the pathogen. A number of deaths were attributed to the outbreak. Currently, there is no drug to treat *Cryptosporidium* infection in humans.[180]

There is additional evidence of significant environmental impacts from STPs including work done under the Ontario government's Municipal/Industrial Strategy for Abatement (MISA) program and the November 1994 report of the Ontario Auditor General on STP operations in the province. The Auditor General's report showed the degree to which Ontario STPs were out of compliance with provincial standards. Some of the MISA documents (e.g., the 1988 report entitled *Controlling Industrial Discharges to Sewers*) provided evidence of harmful substances in STP effluent from industrial discharges. STPs have been identified by MISA and the International Joint Commission as some of the worst sources of pollutants in the Great Lakes. Consequently, the bioremediation industry's view that there is little cause for concern, since the environment has seen the inoculants used in various applications, needs to be reconsidered. There is ample evidence to raise concerns and to justify the extension of the proposed Canadian regulations to the use of NOMs as well as GEMs.

While the proposed Canadian regulations will cover the open release of NOMs in bioremediation applications, U.S. regulations address the issue of risk to human health and environmental safety from such releases in a more roundabout manner. In an interview, U.S. EPA regulators noted that their environmental legislation, the *Toxic Substances Control Act* (TSCA), was promulgated in 1976 and addressed Congress' concern with industrial chemicals. At that time, NOMs (e.g., mined ores and raw agricultural commodities) didn't have to be reported. Regulators wanted to review new chemical substances about to be manufactured for commercial use for the first time in the United States. NOMs would not have to be reported under the premanufacture notification submission. This became part of the precedent. NOMs would be considered implicitly included on the TSCA Inventory of Chemical Substances (similar to CEPA's DSL), and only new chemicals would be reported.

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[179] Newman, Alan. "EPA considering quick action on *Cryptosporidium*." *Environmental Science & Technology*, Vol. 29, No. 1, 1995, p. 17.

[180] Ibid

In the 1980s, when the EPA began to look at living microorganisms, and realized that these could be considered as chemical substances subject to TSCA, a decision was needed regarding NOMs. Interviewees noted that:

> [T]he agency made the decision, for a variety of reasons including the resource issue, that NOMs (just like naturally occurring chemicals) would be excluded from the premanufacture notification requirements and would be implicitly considered to be listed on the TSCA inventory. The agency felt that any new risks that came up regarding NOMs that were already in commerce could be addressed under other aspects in TSCA....the EPA wasn't giving up on NOMs but didn't know of any that needed to be regulated at the time, and none have arisen to change their minds.[181]

As it currently stands, the TSCA Inventory contains all NOMs, certain classes of GEMs and an extremely long listing of biochemicals and biopolymers. This is because the TSCA classifies biochemicals and biopolymers as chemicals, and because the TSCA chemical regulations have been in place for a long time. In contrast, the CEPA's provisional DSL reflects a period (1984 to 1986) during which there was negligible commercial development activity by the Canadian biotechnology industry. As a result, the provisional biotechnology DSL (*Canada Gazette*, Part I, November 20, 1993) contains only one microorganism and nine biochemicals/biopolymers. All other organisms (NOMs or GEMs) and their products, including biochemicals and biopolymers, will fall under CEPA notification requirements.

A Canadian industry spokesperson noted that U.S. regulators consider North America as one territory for the purpose of defining the term "indigenous." That is, proof of an organism's safety in one site would be considered proof of safety anywhere on the continent (even in Canada). In contrast, CEPA regulators have indicated that they will require additional information for NOMs if they are not used in the same habitat. This representative added that these disparities place Canadian biotechnology producers and users at a significant competitive disadvantage because separate evidence would have to be produced for each habitat deemed distinct by CEPA regulators (with corresponding added costs).

A Canadian regulator responded with the view that health and safety assurances must predominate in the absence of scientific proof that the continent is one territory with respect to any given NOM (or GEM). Furthermore, she noted that the proposed biotechnology regulation permits notification for use in all of Canada (Schedule 14). The habitat-specific schedules were intended to provide for reduced and more specific information requirements where appropriate. Biotechnology products that may be regulated under CEPA are frequently living organisms and, therefore, biologically interactive with the receiving environment. Consequently, some precise knowledge of the specific features and structure of the receiving environment must be known in order to develop a reasonable understanding of the likely environmental effects and fate of the organism in question.

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[181] Zeph, L. and E. Clark., U.S. Environmental Protection Agency, personal interview, Washington, DC, February 16, 1994.

TSCA only considers substances manufactured for distribution in commerce, and would be moot on the issue of using on-site NOMs whether they are stimulated native growth in the ground, or removed, cultured and reinjected into the site. On the other hand, CEPA would regulate where the native growth was removed, cultured and reinjected into the site.

Under TSCA, the EPA makes a "no unreasonable risk" finding. This finding is based on a balancing of risk and benefits. Potential risks can be outweighed by the potential benefits of the product. From their traditional chemicals program, the EPA has conducted economic analyses within a framework that weighs risks to workers against benefits to society from the introduction of a specific chemical product. On the other hand, during a telephone interview, two American regulators noted that the "CEPA is more of a zero risk statute."[182]

These regulators noted that other U.S. statutes cover other uses involving NOMs (see Table 5.5). Part of the TSCA's finding for no unreasonable risk concerning the introduction of non-indigenous NOMs is that, for example, the U.S. Department of Agriculture (USDOA) has statutory authority over non-indigenous organisms of all types (through a broad authority provided under the *National Environmental Policy Act*). The 1986 Coordinated Framework for the Regulation of Biotechnology Document (CFRBD)[183] lays out each federal agency's statutes in biotechnology, how they would cover biotechnology products and the corresponding rationales. The EPA will continue to follow its stated position in the CFRBD until the rules provided in the 1992 draft TSCA regulations (which are still restricted and confidential) become final.

The American regulators compared the proposed Canadian and U.S. regulations. They noted that, although the scope of each country's regulations differ (the United States excluded NOMs from regulation, for example), in practice the data requirements which Canada is developing are very limited for low-risk microorganisms. Therefore, the Canadian reporting burden might be very small in those categories. In consequence, although the scope differs, the limited reporting burdens would narrow the difference between the two countries. Nevertheless, this difference, however large or small (a debatable issue), would confer an advantage to American competitors by acting as a disincentive to Canadian investment in the manufacture of affected biotechnology products destined for U.S. markets. Furthermore, unless other trading countries conferred preferential treatment to Canadian biotechnology products which meet the more stringent regulatory requirements, the competitive disadvantage (vis-à-vis comparable U.S. products) would extend to the global market. An Environment Canada official noted that there are reduced information requirements in the proposed CEPA regulations for products destined for export only.

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182 Ibid

183 United States Office of Science and Technology Policy. *Coordinated Framework for Regulation of Biotechnology.* Federal Register, Vol. 51, No. 123, June 26, 1986, pp. 23302-23350.

Some Canadian stakeholders take the opposing view. They contend that the science related to the evaluation of the environmental effects of introduced microorganisms is very much at a developmental stage. In this context, the precautionary approach taken by Environment Canada and Health Canada is prudent and fully justified. They disagree with the suggestion that CEPA is a zero risk statute. The notification regulation is concerned with the determination of "toxicity" (i.e., the identification and characterization of potential risk, which is allowed to be higher than zero without a declaration of toxicity). Some level of evidence of harm or potential harm is required before a product can be declared "toxic." The risk–benefit approach adopted under the TSCA is not mandated under CEPA. In the opinion of some Canadian stakeholders, the TSCA approach is deeply flawed and, in the present context, would place public health and the environment at considerable risk for the economic benefit of a single industrial sector.

In January 1994, the U.S. EPA and Environment Canada sponsored a workshop in Washington on the issue of fate and effects testing schemes for microorganisms.[184] At that workshop, Martin Alexander (Professor in the Department of Soil, Crop and Atmospheric Sciences at Cornell University) presented a commissioned scientific paper calling into question the standard tier testing schemes used to determine the toxicity of chemicals. The paper was a "straw man document" and was intended to stimulate discussion at the workshop. Alexander's conclusion was based on the fact that, unlike synthetic chemicals, living microorganisms replicate, survive, compete and transform in the environment. His paper showed that using end points based on single species of microbes in testing schemes for mixed populations of living microorganisms would be problematic. Indeed, Alexander suggested that traditional testing approaches may provide a false sense of security with respect to the potential environmental effects of an introduced organism, as they fail to capture the full range of potential effects. The results produced at this workshop differed significantly from the discussion paper, however, and interested readers should obtain copies of the proceedings from the Environment Canada sponsors.

The interviewed American regulators also felt it was important to acknowledge that the process of developing environmental regulations was in great flux in the United States, Canada, the European Union and Japan. They noted that Japan was in a more preliminary stage in its development process than any of the other countries. A recent report[185] suggested that the regulatory climate in Japan is, at best, equivocal toward new biotechnology. Japan has adopted a process-based regulatory approach — with special requirements for products derived from rDNA. Several areas have been significantly impeded. The report adds that:

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[184] Landis, W.G., J.S. Hughes and M.A. Lewis (eds.). "Ecological risk assessment under TSCA." *Environmental Toxicology and Risk Assessment*. ASTM STP 1179, American Society for Testing and Materials, Philadelphia, 1993; *Development of ecological tier testing schemes for microbial biotechnology applications*. Prepared by Clement International Corporation, Fairfax, VA., for U.S. EPA and Environment Canada. December 14, 1993. (EPA Contract No. 68-D1-0126); Jaworski, J. *Regulation of biotechnology: report on a joint EPA/ Environment Canada meeting to develop a tiered testing scheme. January 10-13, 1994*. Industry Canada, January 17, 1994.

[185] Kinoshita, June. "Is Japan a boon or a burden to US industry's leadership?" *Science*, Vol. 259, January 29, 1993, pp. 596-598. With responding letter: Miller, H.J. "Biotechnology in Japan." *Science*, Vol. 259, March 19, 1993.

> [D]espite a medical and scientific infrastructure that could support clinical trials of human gene therapy, no Japanese group is close to moving into the clinic, and no Japanese company has been created with gene therapy as its goal. By contrast, gene therapy trials are already under way in the U.S., Italy, France, the Netherlands, and China. Japan's attitude toward the new biotechnology is similarly reflected in agricultural biotechnology. Only a single field trial of an rDNA-manipulated plant has been carried out in Japan (and none of microorganisms), and Japanese R&D in this area is behind what one would expect. The Japanese government has provided little encouragement in the form of clear, predictable, risk-based regulation to those contemplating field trials. Moreover, the Japanese Ministry of Health and Welfare has imposed a strict regulatory regime specific to foods and food additives manufactured with rDNA techniques.

In the United States (and in Canada as well), bioremediation has been used to refer to any biology-based waste treatment methodology, and not just actions using GEMs. Neither the American public, regulators nor remedial contractors have equated biotreatment with genetic engineering. Rather, it has been marketed as a technology relying expressly on NOMs, thus avoiding the stigma of the unfamiliar. Federal laws and regulations influence the development of commercial bioremediation in the United States and reflect the American public's environmental awareness and concerns, all of which encourage the use of NOMs in preference to GEMs.

In the United States, the EPA administers environmental programs based on independently formulated U.S. environmental legislation. The agency's implementation of these laws stimulates the development of markets for commercial bioremediation and controls the applications of environmental biotechnology. Table 5.5 summarizes U.S. legislation affecting the application of NOM-based waste treatment.

It is important to note the much more stringent environmental liability rules in the United States, especially under the *Comprehensive Environmental Response, Compensation and Liability Act* (CERCLA) of 1980, amended by the *Superfund Amendments and Reauthorization Act* of 1986. CERCLA and Superfund establish an environmental liability regime which is retrospective, absolute, and joint and several in the event of environmental damage remediation. No comparable environmental liability legislation exists in Canada at the federal or provincial level.

Retrospective liability refers to the imposition of liability on those who were responsible for contamination of sites in the past, even if they are no longer involved with the property or if the pollution occurred before the enactment of legislation prohibiting or regulating it.[186] Under an absolute liability regime, liability would apply under all of the following.

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[186] Ford G., D. Macdonald and M. Winfield. "Who pays for past sins?" *Alternatives*, Vol. 20, No. 4, 1994, pp. 28-34.

1. The polluting activity was regulated but out of compliance, e.g., on-site land disposal of hazardous waste without the necessary environmental approvals.

2. The polluting activity was unregulated, i.e., the pollution of land occurred before the provinces enacted environmental legislation in the early 1970s.

3. The polluting activity was regulated and the pollution was in compliance with all requirements but contamination still resulted, e.g., duly authorized disposal of liquid hazardous waste in a municipal solid waste landfill before such practices were prohibited.

Under a joint and several liability approach, one party may be held responsible for all the remediation costs, regardless of the party's contribution to the damage. When this is the case, the law usually makes provision for the parties held jointly and severally liable to seek recovery of costs from the other parties who had a role in the contaminating activity. It may also provide for allocation or apportionment of liability.[187]

In Canada, Environment Canada has convened a stakeholder consultative committee to assist its development of biotechnology regulations under CEPA. Committee members are drawn from related federal departments and agencies, provincial governments, environmental industry associations, environmental and public health associations, biotechnology research and industry alliances, academics and labour.

During the evolution of legislation in the United States, public and private organizations (similar to the constituencies in the CEPA consultative process) negotiate with elected officials in order to reflect the positions of their particular constituency.[188] These organizations (industry, national environmental associations and state/local governments), influence environmental legislation. There are four different industry factions, however, each of which has its unique agenda: waste generators, waste managers, the environmental consultants and product vendors, and the engineering and construction firms.

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[187] Ibid

[188] Markland Day, Sue. "US environmental regulations and policies - their impact on the commercial development of bioremediation." *Trends in Biotechnology*, Vol. 11, No. 8, August, 1993, pp. 324-327.

Table 5.5

Major U.S. Environmental Laws Controlling the Use of Biology-Based Waste Treatment

U.S. Federal Legislation	Provisions under the Law
Toxic Substances Control Act (TSCA) of 1976	TSCA requires the review of health and environmental effects of new chemicals and chemicals already commercially available. If a chemical's manufacture, processing, distribution, use or disposal would create unreasonable risks, EPA can regulate or ban it. The Agency adds new chemicals, including GEMs, to its TSCA Inventory to signify its approval for commercialization. TSCA covers GEMs for bioremediation and PCB treatment/disposal processes.
Federal Water Pollution Control Act of 1972 amended by the *Clean Water Act* (CWA) of 1977, and the *Water Quality Act* of 1987	The CWA is the major law protecting the "chemical, physical and biological integrity of the nation's waters." Water quality standards, technology-based effluent limitation guidelines, pretreatment standards and a national permit program to regulate the discharge of pollutants are established under the Act. Under the CWA, it is national policy to prohibit the discharge of toxic pollutants.
Solid Waste Disposal Act of 1965, amended by the *Resource Conservation and Recovery Act* (RCRA) of 1976 and the Hazardous and Solid Waste Amendments (HSWA) of 1984	The RCRA creates a cradle-to-grave regulatory system for hazardous waste and requires the EPA to establish standards, procedures and permit requirements for waste treatment, storage and site clean-up disposal. In addition to banning the land disposal of untreated toxic wastes, the HSWA also authorized a clean-up program for underground storage tanks for petroleum and hazardous substances. The HSWA required all facilities holding a hazardous waste permit to remediate any contaminated soils or groundwater on their property.
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) of 1980, amended by the *Superfund Amendments and Reauthorization Act* of 1986	Under CERCLA, EPA can remediate polluted sites using money from a hazardous waste superfund and then sue responsible parties to recover the money.
Clean Air Act (CAA) of 1970, amended by CAA Amendments of 1977 and 1990	The CAA requires the EPA to set national ambient air quality standards for common and widespread pollutants and for air toxics.
National Environmental Policy Act (NEPA) of 1969	The NEPA was enacted January 1, 1970 and requires the federal government to develop environmental impact statements (EISs) before undertaking any major federal actions. An EIS is a detailed evaluation of the proposed federal action which is open to public review and comment. It should include discussions of the purpose of, and need for, the action, alternatives, the affected environment and the environmental consequences of the proposed action. For example, if a GEM were to be released on federal property, then an EIS could be required.

Source: Markland Day, Sue. "U.S. environmental regulations and policies —- their impact on the commercial development of bioremediation." *TIBTECH*. Vol.11, August 1993, pp. 324-328.

The American bioremediation industry has its first opportunity to influence the structure of U.S. environmental programs through meetings at the political level when legislation is first being contemplated. In the 1980s, the environmental treatment industry and environmental groups joined together to advocate source reduction and treatment as the waste management practices of choice.

Once legislation is passed and enacted, the EPA is delegated the responsibility to write policies and regulations implementing new environmental programs or amending existing programs as specified by the law. The regulations are very detailed, legally enforceable and govern EPA–industry interactions. In the water, air, pesticides and toxics programs, these informal discussions commonly occur during the drafting of regulations. In the solid and hazardous waste program, state regulators and environmental groups dominate the regulatory development process.[189] This is not surprising given that solids and hazardous waste sites are fixed and local concerns while air, water and the other areas are global in scope. New regulations are published in the *Federal Register* as "proposed rules" and provide stakeholders with an opportunity for comment. In turn, the EPA is obliged to publish these comments, its response to the comments and the final regulation in the *Federal Register*. Debate on the final rule then passes to the court system. Once regulations have become final and have been field tested, the EPA writes guidelines and policies to clarify, for the enforcers (usually state environmental regulatory agencies) how the regulations apply in practice.

The Canadian process of developing regulations is similar, and the proposed NSNR for biotechnology products is no exception.

Four American states (Minnesota, North Carolina, Texas and Wisconsin) have enacted biotechnology statutes with associated regulations and with oversight boards. These state boards have additional powers to approve biotechnology products for use within their jurisdictions. In addition, local (i.e., municipal and county) authorities have exercised control selectively over the years to ban particular products from sale within their boundaries.

Ontario has had a number of ongoing initiatives to develop biotechnology regulatory policy.[190] In 1993, the Premier's Council on Health, Well-being and Social Justice announced a provincial policy target to "develop and implement programs to minimize any risks associated with the testing, production and use of biotechnology products."[191] Goals include:

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[189] Markland Day, Sue. "US environmental regulations and policies - their impact on the commercial development of bioremediation." *Trends in Biotechnology*, Vol. 11, No. 8, August, 1993, pp. 324-327.

[190] Government of Ontario. *Biotechnology in Ontario - Growing safely.* Government of Ontario Green Paper, September 1989. ISBN 0-7729-6074-7.

[191] Government of Ontario. *Our Environment, Our Health: Healthy Ecosystems, Healthy Communities, Healthy Workplaces.* Premier's Council on Health, Well-being and Social Justice. Report of the Review Committee on Goal 3. January 1993.

- to develop a strategy designed to regulate and control biotechnology activities that are potentially hazardous;
- to require producers to maintain parent stock (e.g., gene bank);
- to develop guidelines for responding to environmental emergencies caused by the uncontrolled release of genetically engineered living organisms;
- to support research to determine the impact the release of GEMs will have on human health and the environment; and
- to increase public confidence in the biotechnology industry by educating industry and consumers about the hazards associated with the release of GEMs and the steps being taken to control risks and prevent harm.

Recently, Ontario's Green Industry Ministerial Advisory Committee (GIMAC) announced a strategy to identify initiatives to strengthen the competitiveness of the province's green technologies and environmental businesses. Among its recommendations was the development of an environmental technology certification process to assist in establishing the effectiveness and safety of new environmental technologies to support the development of domestic and export markets.[192] Similar programs are under development in California and Massachusetts.

With the recent enactment of the *Alberta Environmental Protection and Enhancement Act* (AEPEA), that province has exercised its option to regulate certain biotechnological activities within its boundaries. According to the AEPEA, the province must issue an approval before the construction, operation or reclamation of a plant for the manufacture or use of biotechnology products. A biotechnology manufacturing plant is defined in the regulations as a plant that produces products using the application of science and engineering in the direct or indirect use of living organisms or parts, or products of living organisms in their natural or modified form [which is identical to the CEPA definition of biotechnology, section 3(1)], but does not include a facility that engages solely in research.[193]

While this definition is broad enough to include bakeries and breweries, it would seem unlikely that the province wants to cast the regulatory net so wide. The Alberta government has yet to issue any regulations or guidelines specifying what biotechnology operations will require approvals or what information must be submitted to obtain such an approval.

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[192] Government of Ontario. *Green Industry Sector Strategy for Ontario.* The Green Industry Ministerial Advisory Committee (GIMAC), April 1994.

[193] Lewis, G.M. *Alberta regulates biotechnology through new environmental legislation.* Dr.Glennis M. Lewis, Ogilvie & Co., Edmonton, Alberta.

British Columbia is contemplating legislation to regulate genetically modified organisms. The proposed B.C. environmental protection act contains provisions for regulations to control both traditional and recombinant technologies, the genetically modified organisms constituting the products of those technologies, as well as the acquisition, release or marketing of the products within the province.[194] The legislation is an estimated one year away from consideration by the province's legislature. Its evolution and its impact on the development of B.C.'s environmental biotechnology industry will be of keen interest to that industry and to other Canadian stakeholders.

In several respects, Canada's proposed environmental regulations for its biotechnology industry are more stringent than those of most of its major trading partners, the United States in particular. First, Canada is the only jurisdiction to incorporate NOMs in its biotechnology regulations. Second, the draft regulations include products of living organisms (including biochemicals and biopolymers) unlike other major trading partners, e.g., the United States. Third, CEPA's DSL only contains products reported to have been in manufacture or importation during the 1984 to 1986 period when very few biotechnology products were available in Canada. In contrast, the U.S. Inventory has been growing since TSCA legislation was promulgated in 1976. Because the chemical regulations (which cover biochemicals and biopolymers) were first to be developed under TSCA, the Inventory now contains a large and growing number of such products. While the DSL will grow with the addition of products falling under the transitional provisions (and afterward), there will be reporting costs for Canadian companies which could jeopardize the competitive position of their products in Canadian commerce. Finally, the CEPA regulations require additional proof of product safety with changes in habitat. Comparable U.S. regulatory provisions accept scientific evidence of safety in one habitat as applicable to all continental habitats including Canada.

Canadian regulators have argued that "strict, anticipatory regulatory standards can be a potent force in stimulating innovation and upgrading in industry, provided they are designed and administered effectively."[195] This has been generally true for chemical contaminants, and the United States is a prime example of successfully developing environmental technology exports in response to stringent environmental legislation. However, it is important to consider the history of the chemical and allied industries responsible for the chemical pollution. The harmful aspects of many chemicals on health and the environment were not recognized until the industry was mature, and much environmental damage had been done. In fact, in many cases analytical techniques were not sensitive enough to detect contamination at levels which were recognized to cause harm. As both analytical techniques and environmental risk determination improved, the harm was identified and

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[194] "Excerpts from proposed B.C. Environmental Protection Act." Table of contents and extracts from Part 7 on genetically modified organisms. Draft dated January 19, 1994.

[195] Blain, Robert. *Canadian competitiveness and environmental standards.* Regulatory and Economic Affairs Division, Environment Canada, November 4, 1991.

regulatory standards were tightened.[196]

The recent development of biotechnology has followed a different path. Potential hazards were identified in advance and dealt with immediately.[197] For example, a moratorium was placed on laboratory genetic engineering until the risks were better identified. As knowledge grew, containment procedures were relaxed. A similar process has governed the field release of agricultural biotechnology products. In contrast to the chemical industry, biotechnology industrial development has been cautious and knowledge based from its beginning in the early 1970s. As scientific evidence accumulated to warrant a relaxation of precautions, these requirements have been removed leaving only those considered necessary to safeguard human health and environmental safety.

A Canadian industry representative argued that stringent environmental standards will only delay technology innovation and place Canada at a competitive disadvantage to those countries which react quickly to evidence of limited risk by developing newer standards (selectively applicable to the real hazards as they are identified) and removing controls where necessary.[198]

This viewpoint, however, is weakened by the fact that Canadian environmental biotechnology firms lack the industry associations or other organizations to implement voluntary standards. In addition, Porter and others have argued that there is a positive impact from well-designed regulations on competitiveness. Porter's point is that strong standards, in addition to protecting human health and the environment, require the development of high-quality products. Products which meet standards which are internationally recognized as high are also less likely to have difficulty entering export markets.

Some groups argue that the most significant barrier to the development of the Canadian environmental remediation sector is the lack of clear decision-making processes and liability rules regarding the remediation of contaminated sites in Canada. The failure to establish effective means of financing the remediation of "orphaned" sites is also a major problem.[199] Furthermore, under the terms of the National Biotechnology Strategy (NBS) announced in 1981, five strategic areas were announced for federal government support including the pollution control and waste treatment sector. All sectors started off on equal footing in terms of opportunities provided for them under the strategy and for access to NBS research funds. All had the same degree of federal support. The failure of this sector to get out of the starting blocks quickly can be attributed to any number of factors including:

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196 Gannon, D.J., Zeneca Bio Products. personal communication, April 11, 1994.

197 Organization for Economic Co-operation and Development. *Biotechnology: economic and wider impacts*. OECD, Paris, 1989.

198 Gannon, D.J., Zeneca Bio Products. personal communication, April 11, 1994.

199 Ford G., D. Macdonald and M. Winfield. "Who pays for past sins?" *Alternatives*, Vol. 20, No. 4, 1994, pp. 28-34

- institutional inertia, both government and private sector;
- perceived low market glamour of the products in the international market place;
- the diffuse geographical locations of industrial activities in these areas; and
- the lack of an industrial association/national lobby.

In comparison, the impact of the proposed CEPA regulations seems likely to be marginal. Indeed, if these broader policy questions are resolved, the market for firms capable of providing safe and effective environmental remediation technologies is likely to be extremely favourable.

5.5 Environmental Biotechnology-Related Subsidies and Programs

As noted earlier, biotechnology development takes place along a science push to market pull trajectory. As has been true for the health care and agri-food sectors, the spawning of environmental biotechnologies will be driven largely by scientific research initiatives. These initiatives will emerge from clusters of working Canadian scientists and fledgling technology development enterprises. These clusters produce biotechnologies to improve the environmental performance of Canadian and global industries. They also provide a training ground for the labour force which will develop and apply these technologies.

In 1989, the Canadian Council of Ministers of the Environment initiated the five-year, $250 million National Contaminated Sites Remediation Program (NCSRP).[200] The goal was to deal with properties across the country that had been polluted with hazardous materials originating from industrial or commercial activities. In each case, the NCSRP's concern was to ensure that appropriate clean-up of the site occurred where contamination was a serious threat to human health or environmental quality.

The NCSRP has been administered through bilateral agreements between the federal and participating provincial/territorial governments. A total of $200 million has been committed toward orphan site clean-up and $50 million toward technology development and demonstration projects. Some five of the 26 orphan site projects commissioned under the NCSRP are deploying some form of bioremediation technology (according to NCSRP's 1992-1993 Annual Report). In addition, the Development and Demonstration of Site Remediation Technology (DESRT) component of the NCSRP shows that 14 of its 24 projects involve the development or demonstration of bioremediation technologies.

Under Canada's Green Plan, in 1990 the Clean Air Technologies Division was formed within Environment Canada.[201] The Division's mission is to stimulate R&D and demonstration projects, provide information and develop partnerships and networks to

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[200] The National Contaminated Sites Remediation Program. *1992-1993 Annual Report. Canadian Council of Ministers of the Environment.* CCME-Secretariat, Winnipeg, Manitoba. ISBN 1-895925-02-9.

[201] Murray, K.J. *Strategies to stretch your R&D dollar.* CCH Canadian Limited, North York, Ontario, 1993.

promote and develop clean air technologies including biotechnologies. A report from a representative of the Division noted that opportunities exist for importing European biotechnologies (viz., for treating industrial off-gases), adapting their use for North American climates and marketing the products throughout the Americas and beyond. Canadian companies can adapt the technologies, manufacture and apply them in this country.

Canada's Green Plan has also created a number of federal programs through which individual Canadians, businesses, groups, colleges and universities may obtain financial support for projects to improve the environment. There are undoubtedly some biotechnology activities in motion under the Plan.

Several provinces have co-ordinated programs (with Environment Canada) and stand-alone programs under way to provide R&D and demonstration project funding for environmental improvement. Ontario's Ministry of Environment and Energy has several such programs including: the Contaminated Sediment Treatment Technology Program (COSTTEP) to foster development and demonstrate technologies to remediate contaminated sediment; the Great Lakes Cleanup Fund; and the Mine Environment Neutral Drainage - Ontario (MEND-O) to mitigate acid production from mining sites and prevent damage to large areas of the aquatic and terrestrial environment.[202] Ontario also has the R&D Super Allowance (run by its Ministry of Economic Development and Trade) to provide an additional 25 percent deduction of R&D expenditures for large firms and 35 percent for small businesses. This provides some stimulus to bioremediation technology development activity in the province.[203]

Quebec has established an environmental research and technological development fund (Fonds de recherche et de développement technologique en environnement) providing some $50 million over five years for projects providing preventive and remedial effects on the environment in three priority areas: waste management, pollution control and restoration, and sustainable development. The fund is part of a competitive, integrated government strategy on technological R&D to stimulate technology transfer between research organizations, industry and the government which will contribute toward environmental, technological and economic progress for the province.[204]

A publicly funded and highly visible project was initiated in 1990 to determine the feasibility of bioremediation and other technologies for decontaminating the estimated two million tonnes of contaminated soil in the Port Industrial District (PID) lands of the Toronto

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202 "Funding Programs for the Environment." Draft. Ontario Ministry of Environment and Energy, February, 1993.

203 Murray, K.J. *Strategies to stretch your R&D dollar.* CCH Canadian Limited, North York, Ontario, 1993.

204 *Investing in our future.* (92 0054). The Environmental Research and Technological Development Fund. Ministère de l'Environnement, Québec; Le fonds de recherche et de développement technologique en environnement; Les projets d'innovation technologique en evironnement: normes et description; Votre projet de recherche exploratoire en environnement: guide de présentation d'une proposition. ISBN 2-550-21784-5. Gouvernement du Québec, 1991, 1993.

waterfront. A demonstration project followed in 1991 and 1992 to integrate soil washing, metal removal (by chelation) and organics reduction (by aeration bioreactors) technologies to achieve decontamination and to enable reuse of the soils as clean backfill within the PID.[205]

As a result of the project, it was concluded that the soil washing operation could concentrate contaminants to enable further treatment for reduction of heavy metals and organics. The heavy metals removal technology was flexible enough to permit the extraction and removal of any desired level of metals, and the aerobic bioreactors were very effective in reducing the level of organics in the slurry. As well, the bioreactors provided a cost-effective treatment for the reduction of organics from oil refinery soils and were recommended for use in a full-scale soil treatment centre. Such a centre could treat 50 to 60 tonnes per hour at a cost of about $110 per tonne, provided the facility operated continuously and processed 300,000 tonnes of contaminated soil per year. The project report added that "at a cost of $110/t the cost of soil treatment is competitive with the cost of disposing of contaminated soils in licensed landfills operated by the Municipality of Metropolitan Toronto."[206]

When comparing the tax incentives which exist in both Canada and the United States, it is considerably less costly on an after-tax basis to perform R&D in Canada.[207]

During 1985, the federal government introduced a comprehensive package of R&D incentives designed to replace the Scientific Research Tax Credit mechanism. With subsequent amendments, a range of tax incentives has been created for corporations conducting R&D that is the richest available in any major industrialized country. These tax incentives represent approximately 65 percent of the federal government's contribution to R&D. In addition, several provincial governments also offer tax incentives for R&D performers. These incentives, when combined with federal and provincial grants, can significantly reduce the cost of performing R&D in Canada.

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205 Mourato, D. and D.D. Lang. *Final report on the Toronto Harbour Commissioners' soil recycling demonstration project. Summary of operations and test results,* December 1993.

206 Ibid

207 Murray, K.J. *Strategies to stretch your R&D dollar.* CCH Canadian Limited, North York, Ontario, 1993

CHAPTER 6

INTELLECTUAL PROPERTY RIGHTS

This chapter explores the economic impact of current levels of intellectual property (IP) protection for biotechnology inventions on the ability of Canadian biotechnology firms to finance research and development (R&D), and to gain access to foreign technology. Where possible, we have identified Canada's interests in this policy area and advised on optimal Canadian strategies for IP protection in the light of both industry and consumer interests. Research is based on interviews (with IP practitioners, representatives of the Canadian biotechnology industry, technology transfer officials in universities and consumer spokespersons) and a review of the published literature on IP and biotechnology inventions.

6.1 Patent Law and Biotechnology

Patent law is one category of intellectual property rights which also covers trademarks, industrial designs, plant breeders' rights and copyright. The law of intellectual property, both national and international, is based on written statutes and case law which establish what sorts of invention and innovation may be protected and the procedure for securing the appropriate protection. Trade secrecy provides the main alternative method to patents for ensuring protection against piracy or imitation of ideas and valuable new technology.[208]

Biotechnology is rooted in classical microbiology, for which trade secrecy has often provided sufficient protection for the industrial innovator. But second generation biotechnology has extended into areas in which patent protection has proven attractive to scientific and business enterprise. The traditions of patent law predate second generation biotechnology by almost 100 years with the Paris Convention of 1883 being a notable milestone in the international development of patent law. Its general concepts apply to a whole range of inventions of which microbiological invention is only one part. Nevertheless, there are special official regulations governing procedural matters for the patenting of microbiological inventions, e.g., the deposition of new strains in culture collections for patent purposes which falls under an international convention, the Budapest Treaty. In addition, there is a substantial volume of case law on the subject.

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[208] Crespi, R.S. "Microbiological Inventions and the Patent Law - the International Dimension." *Biotechnology and Genetic Engineering Reviews*, Vol. 3, September 1985, pp. 1-37; Crespi, R.S. "Microbiological Inventions and the Patent Law - International Developments." *Biotechnology and Genetic Engineering Reviews*, Vol. 7, December 1989, pp. 221-258; Crespi, R.S. "Biotechnological Inventions and the Patent Law: Outstanding Issues." *Biotechnology and Genetic Engineering Reviews*, Vol. 11, December 1993, pp. 229-261; Crespi, R.S. "Biotechnology and Intellectual Property. Part 1: Patenting in Biotechnology." *Trends in Biotechnology*, Vol. 9, April 1991, pp.117-122; Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp.151-157.

6.1.1 The Nature of Patents

A patent is a form of property right granted by the appropriate state authority in respect of an invention. It is legally enforceable by its owner against unauthorized exploitation by others. To obtain patent protection in Canada, an application must be made to the Canadian Intellectual Property Office (CIPO). This is usually done by the inventor or whoever claims the ownership and benefit of the invention. The patent application will be officially examined and, after a process of negotiation between the applicant and the patent examiner, it will be accepted or rejected. This examination is principally concerned with the written specification of the invention, which must be filed with the application and which must define the scope of the protection sought (i.e., the claims of the patent).

There are four basic requirements for patentability, three of which the invention itself must fulfil, i.e., it must have novelty, non-obviousness and practical utility or industrial applicability. The fourth requirement concerns the specification. This must be adequate in content to enable those of ordinary skill and experience in the field to follow the directions and obtain the promised results. The application of these criteria in practice often involves legal subtleties.

Novelty

To fulfil this condition, the invention must not already be available to others by any kind of public disclosure or use before the date of filing of the patent application. Although the rule is commonly expressed in terms of publication, it is important to note that this includes *all* forms of public disclosure and is not limited to literature publication. It also covers use prior to the patent application, even those made by or due to the inventor himself or herself! All such prior knowledge, is known as the "state of the art" or "prior art." Prior experimental use which occurs within the privacy of the research laboratory is not part of the state of the art as long as the details remain as private or restricted information. A disclosure by an inventor can sometimes be confidential, as distinct from public, and this does not destroy novelty. While this strict novelty rule applies to most countries, the United States, Canada, Japan and a few other countries are exceptions in that they allow grace periods for filing patent applications in their respective countries after publication or use by the inventor.

Non-Obviousness

The invention must not be "obvious" to the ordinary skilled worker over the state of the art, i.e., it must not follow plainly or logically from what is already known. Research workers who write literature publications which present their work as a natural logical scientific development from prior published papers make it difficult to argue that it has inventive character.

Utility or Industrial Application

Utility is a crucial concept in U.S. patent law but is not limited to industrial utility. Any other sort of practical utility can suffice. In Canadian as well as European law, an invention must be capable of industrial application.

Adequate Disclosure

The description of the invention must permit repetition of the work by a person of normal skill in the art. This criterion has led to special problems with biological inventions in that it is often difficult, or even impossible, to define living organisms or their products with sufficient precision to ensure reproducibility.

These four criteria can be interpreted in different ways by different national patent authorities, and interpretations by patent offices evolve over time to meet new requirements or are modified in light of new rulings of courts of law. For such reasons, there are differences in patent law and its interpretation in various countries although international agreements have done much to minimize these inconsistencies.

6.1.2 Scope and Types of Patent Protection

A patent confers a monopoly without establishing, of itself, a situation which can be described as monopoly. That is, a patent gives a holder the right to exclude others from making, using or selling a *particular* invention for a limited period of time. It does not monopolize anything more than the specific invention, does not preclude alternative and different methods of solving the same problem and is not anti-competitive. On the contrary, it stimulates competition and the search for ways to "design around" the patent. It is a reasonable right to allow to those who invent and enrich the state of the art. Moreover, the right is conditional on any prior and wider-embracing rights which may be held by others and is not an automatic guarantee of the freedom to use one's own invention. However, the issuance in Canada and other countries such as the United States of broad blocking patents (discussed in Sect.6.3.1) for "pioneer" biotechnology products and processes can be viewed as anti-competitive behaviour and a threat to the commercialization of other innovations in areas covered by these patents. The precise extent of the right in technological terms is governed by the patent claims, a topic to be discussed below. The writing of a patent specification is always a highly individual work tailored to the particular invention and the experimental data available. Inevitably, however, a certain stereotype structure acceptable to patent offices has emerged over many years. It is standard practice:

- to state the problem at which the research has been aimed;
- to discuss and assess previous attempts to solve it;
- to describe the novel particular solution in broadest terms;

- to provide data and worked examples to instruct the reader in how to apply the invention in practice (The extent to which the invention is exemplified by actual data covering a wide range of possible applications is crucial in determining the scope of the claims that will be granted); and
- to present claims defining the scope of protection sought.

Patent Claims

The claims of a patent have a purely legal function and, although this is not precisely the same under all national patent systems, it is broadly true that the wording of the claims is a guide to the scope of protection obtained. It is for the applicant to devise these claims and to do so wisely in order to cover all conceivable methods, forms and embodiments in which the invention can be exploited commercially. If this is not done comprehensively, the patentee cannot assume that a court of law will subsequently fill in for him or her the gaps left in the protection inadvertently or through lack of foresight.

The applicant, usually through a patent agent, argues the case with the patent office examiner, and strives for allowance of the broadest possible claims and the greatest variety of claim types to ensure that the applicant's interests are properly protected. In this the applicant does not have unlimited freedom, because the claims must be "supported by the description." Therefore, the experimental data and technical teaching in the specification provide some check on how many different types of claim can be obtained and what their scope may be.

Types of Claims

The most usual forms of claim in microbiology are claims to new processes, products, compositions and uses. These are written in the form now well established for chemical inventions. Indeed, there is a considerable body of precedent in the case law of chemical patents that has been taken over into its microbiological counterpart.

The Product Claim: Product claims are of two main types:

- the product per se claim which extends to a substance or microorganism as such and is independent of any defined process of preparation or derivation (Such a claim is said to provide absolute product protection.); and

- the product-by-process claim which defines a substance or microorganism in terms of some particular method of production. Hence, the product-by-process claim is of more limited scope than the per se claim and can be avoided by using a production method differing from that defined in the claim.

The product per se claim is available only when the product is a new substance, i.e., not disclosed or available to others by any kind of public disclosure or use before the date of filing of the patent application. Prior written or oral disclosure of a compound or any other invention, and any other method of making the knowledge available in a public manner before seeking patent protection makes it part of what is termed the "prior art."

The product-by-process claim is used primarily when the novelty lies in the process, the product itself being known from earlier work and obtained by some previous process. Sometimes this form of claim has to be used when the product is, in fact, new but is of such complex and imperfectly known constitution that it cannot be adequately characterized in a product per se claim. Difficulties of this kind arose when the first attempts were made to patent enzymes and other large molecules including those produced by other technology, e.g., synthetic polymer chemistry. The definition of a substance in terms of biological function alone was usually not accepted by Patent Office examiners conditioned by many years of experience with inventions in the field of simpler organic chemistry.

The Discovery of Biologically Useful Properties in a Substance Already Known in Itself: This type of invention can be protected by means of a claim to a composition in which the known substance is present as an active ingredient, e.g., a pharmaceutical or insecticidal composition. An alternative to claiming the composition might be to claim the actual new use of the known substance, but this cannot be done if the use is medical because of the specific exclusion of methods of medical treatments as patentable subject matter in most countries, the United States being the most notable exception. Canada is apparently also an exception in that there have been cases where new therapeutic uses of known compounds (that are in essence methods of medical treatment) have been granted protection by the Canadian Intellectual Property Office (CIPO). In at least two cases [*Re Application for Patent of Wayne State University* (1988), 22 C.P.R. (3d) 407; *Re Application for Patent of Merck & Co Inc. (now patent No. 1,294,879)* (1992), 41 C.P.R. (3d) 52], the fact that the subject matter of the applications related to a new therapeutic use (i.e., method of medical treatment) was not discussed. A further drawback to claims for uses of the invention would be that, generally, the direct infringer of the claim would be the doctor, farmer or other end user, and legal action against these would not usually be worthwhile or desirable. For the patentee, the preferred target is normally the commercial manufacturer or distributor who is infringing the patent.

New Methods of Various Kinds: These comprise another noteworthy group of inventions in the context of patent claims. A method of processing of an industrial material is clearly an acceptable form of claim, as is a claim for a method of testing where the method is applicable to manufacture in some way. Methods of assay were considered of uncertain patentability some 20 years ago, or it was considered slightly unethical to patent them, but these are now regularly patented and successfully licensed or otherwise exploited in the developing field of diagnostics.

6.1.3 The Plant Breeders' Right

While the United States enacted the *Plant Patent Act* of 1930 for the special protection of asexually produced plant varieties, the international system of plant breeders' rights did not come into being until 1961 in response to the demands of plant breeders for a protective mechanism which would ensure a financial reward for them for the long and uncertain process of developing new varieties. Theoretically, the patent system might have been used to meet these demands, but it was considered unsuited both to the technology of the breeding process and to the interests of the industry. It is an essential part of the patent procedure for the inventor to supply a written specification of the new process or product being patented from which it can be reproducibly performed or obtained. Although patents for agricultural machinery (which can be exactly defined) are commonplace, it was felt unrealistic to try to describe breeding/selection processes through detailed written protocols. The industry was simply not ready for patents which required a precise definition of the organisms used or the products derived from them.

Against this background, and because a plant is a self-reproducing entity that can give rise to an indefinite number of descendants and quantity of consumption material (i.e., product, harvest or offspring), legislators deliberately restricted the scope of plant variety protection. Thus, the line was drawn by reference to *propagation* and the *intention* of the propagator of the new variety. The nature of the exclusive right was defined in terms of the production and sale of the reproductive material of the plant variety.

Systems of plant variety rights of the kind described above were created under the national laws of various countries. An international convention governing them, the International Convention for the Protection of New Varieties of Plants (UPOV), was drawn up in 1961 and took effect in 1968. The UPOV Convention was revised in 1972, 1978 and 1991. Most member states, including Canada and the United States, have acceded to the 1978 revision. The 1991 revision specifies seven acts of exploitation for which the breeder's authorization is required:

- production or reproduction (multiplication);
- conditioning for the purpose of propagation;
- offering for sale;
- selling or other marketing;
- exporting;
- importing; or
- stocking for any of these purposes.

The 1991 revision specifies four subject matters to which breeders' rights extend:

- the protected variety itself;
- varieties not clearly distinguishable from the protected variety;
- varieties essentially derived from the protected variety; and
- varieties whose protection requires the repeated use of the protected variety.

The 1991 revision further specifies that these exclusive rights must extend not only to propagating material but also to harvested material that has been obtained through the unauthorized use of propagating material when the breeder has had no reasonable opportunity to exercise his right in relation to the propagating material.

Article 15(2) of the 1991 revision provides that:

> each Contracting Party may, within reasonable limits and subject to the safeguarding of the legitimate interests of the breeder, restrict the breeder's right in relation to any variety in order to permit farmers to use for propagating purposes, on their own holdings, the product of the harvest which they have obtained by planting, on their own holdings, the protected variety.

This provision entitles states, on an optional basis, to except the planting of farm-saved seed from the requirement for the breeder's authorization (the "farmer's privilege"). Also, apart from a special provision relating to the production of ornamental plants or cut flowers, the mandatory minimum scope of protection is limited to the reproductive or vegetative propagating material. Article 15(1)(iii) of the 1991 revision provides that "acts done for the purpose of breeding other varieties" are compulsorily excepted from the breeder's right. The authorization of the breeder is not required for the use of a protected variety as an initial source of variation for the purpose of creating other varieties (the "breeder's exemption").

However, article 14(5) of the 1991 revision provides that a variety which is essentially derived (a term for which the article provides a non-exhaustive list of examples) cannot be exploited without the authorization of the breeder of the protected variety. The existence of this new principle should ensure that innovators in the field of plants will reach agreement before they undertake activities which could result in varieties that are essentially derived from protected varieties. It is hoped that, in the majority of cases, amicable arrangements will be made between plant breeders and/or biotechnologists.

Also under the 1991 revision, a contracting party (viz., member state) is free to protect varieties, in addition to the grant of a breeder's right, by the grant of other titles, particularly patents. Last, article 19 provides a minimum period for the breeder's right of 25 years for trees and vines and 20 years for all other species.[209]

In seeking protection for a plant variety, the most important part of the process is concerned with the examination of the biological material itself on behalf of the public body responsible for granting or refusing the application. Extensive field trials are necessary to determine whether the variety meets the four legal requirements of novelty, distinctiveness, uniformity and stability (the latter three replace the patent requirements of utility and non-obviousness). It is also necessary for the breeder to supply an objective description of the

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[209] Greengrass, B. "The 1991 Act of the UPOV Convention." *European Intellectual Property Review*, Vol. 12, 1991, pp. 466-472.

new variety and to list its characteristics in a qualitative or quantitative way by means of which it is distinguished from previously known varieties. One can think of a plant variety as a "description" to which a particular plant must conform within a range of defined characteristics. These characteristics may be similar to the competent parts of a patent claim, but the comparison should not be pressed too far.

Unlike the procedure described above, the process of obtaining patent protection depends almost entirely on examination of the written word. In the case of microorganisms and other living matter, it is usually necessary to deposit a culture of a new organism in an official culture collection, but this is essentially a supplement to the written specification, which may itself be insufficient as an "enabling disclosure." The prime function of the specification is to describe the invention in a way that a person of ordinary skill in the art can reproduce the invention. In addition, the specification contains the patent claims which define the scope of the invention.

Plant variety protection is highly specific to the particular variety, and its scope is limited by reference to the physical (propagating) material itself combined with the description of the variety including its origin and breeding history as given in the documentary grant of the rights. As the difference between the novel variety and prior known varieties may not be very great, the narrowness of the protection is reasonable and acceptable to the breeder. Another difference between plant variety rights and patent rights is that the former give no protection for enabling technology. Because the plant variety right protects only propagating material, it does not cover process technology, i.e., any novel technique for the production of new varieties, especially where applicable to a wider range of plant materials than the individual variety of a particular species.

6.1.4 The International Dimension

Patent law has a long tradition of international co-operation to solve problems which are not confined to one or a few countries. The most celebrated example is the Paris Convention of 1883 (U.N.T.S., No. 11851, Vol. 828, pp. 305-388), of which there are now over 100 member states (including Canada) and which establishes the basic principle of equal treatment for domestic and foreign inventors. When inventors working in different countries seek to patent the same invention, the Convention allows an international priority to be claimed based on the filing of a patent application initially in one member state and subsequently in others. The notion of a priority date obtained in this way is very important in patent law because, for almost all countries, the party with the earliest date wins the contest, subject to certain provisos.

The main instrument of international collaboration in these matters is the World Intellectual Property Organization (WIPO), based in Geneva, which administers the Paris Convention and other international intellectual property conventions. WIPO often takes the initiative, or is sometimes prompted by a member state, to address a particular problem area, but the results of its work must be ratified by member states and introduced into their national laws if they are to be effective. Once a member state ratifies a convention, it can be required to

comply fully with its provisions but, in practice, WIPO does not act as an enforcement agency.

In more recent times, the next international grouping of major significance to come into existence in the field of patents was the European patent system. The legal basis of this system is the European Patent Convention (EPC) of 1973 which began operation in 1978, and now has 14 member states. All members of the European Union (EU), except Portugal and Ireland, belong to the EPC. Some non-EU states (Austria, Sweden and Switzerland) also belong. The EPC has the distinction of being the first patent statute to introduce specific provisions for biotechnology inventions. One of these concerns the use of culture collections as patent depositories for the placement of microorganisms referred to in patent applications. Another provision deals with the exclusion, from patentability, of plant or animal varieties or essentially biological processes for the production of plants or animals. These particular provisions have been highly controversial from the outset and continue to be hotly debated.

Since the early 1970s, there has been general recognition of the fact that biotechnology is a special case. First, living material is complex and difficult to describe with the precision required by current patent law when writing a specification which enables workers of ordinary skill in the art to put the invention to practical use. In short, this problem is one of "reproducibility" from the written description and has led to the practice of depositing the relevant biological material in a culture collection as a supplement to the written text. Another problem stems from the nature of biological material itself, which can be replicated in vast quantities from minute amounts of starting material. Because of this, the loss of legal control of proprietary biological material can have serious consequences for the proprietor. A third problem is that of variability on continued replication of original biological material and the question of "sameness" between ancestral material and its descendants after multiple generations.

Through WIPO, the practice of depositing microorganisms for patent purposes became international in the Budapest Treaty of 1977 which came into force in 1980. Under this Treaty, culture collections can apply to be officially recognized as "international depositary authorities" (IDAs) in which material may be deposited for these purposes. Any IDA in any member state can be selected by the patent applicant for the deposit of the relevant biological material, and this deposit will suffice for all member states in which the applicant files for patent protection. Canada is not as yet a signator to the Budapest Treaty.

Table 6.1

Key IP Legislation Protecting Lifeforms

United States	Europe	Canada
Patent Act - July 19, 1952, c. 950, 66 Stat. 792, coded at 35 U.S.C. §§101-157 *Plant Patent Act* - May 23, 1930, c. 312, §1, 46 Stat. 376 coded at 35 U.S. C. §§ 161-164 (Asexual reproduction of plants) *Plant Variety Protection Act* - December 24, 1970, Pub. L. 91-577 Title I, §1, 84 Stat. 1542 coded at 7 U.S.C. §§ 2321-2582 (Sexual reproduction of plants) *Orphan Drug Act* - January 4, 1983, Pub. L. 97-414 (drugs and treatments of rare diseases) *Uniform Trade Secrets Act,* 14 U.L.A. 537-51 (1980 and Supp. 1986) (federal requirement to implement at the state level)	*European Patent Convention* - October 5, 1973, in (1974) I.L.M. 270-351 (microorganisms, cell lines, plants and animals, excluding varieties) *International Union for the Protection of New Variety of Plants (UPOV)* - December 2, 1961, in 815 U.N.T.S. 89 (plant varieties).[a] National trade secrets legislation: Germany: *Gesetz gegen den unlauteren Wettbewerb*, June 7, 1909 (RGBI. S. 499), § 17. France: *Code Civil*, art. 1382.	*Plant Breeders' Rights Act* - S.C. 1990, c. 20 (plant varieties) *Patent Act* - R.S.C. (1985), c. P-4, amended byS.C. 1993, c. 151 and S.C. 1993, c. 44 (microorganisms and cell lines) Provincial trade secrets protection: Common law provinces: torts Quebec: *Code civil du Québec*, sections 1457, 1472 and 1612.

Note:[a] Founding member countries of the UPOV Convention are Belgium, Denmark, France, Germany, Italy, the Netherlands, Switzerland and the United Kingdom.

Source: Research compiled by the staff in the Intellectual Property Policy Directorate, Industry Canada.

Despite the fact that the United States and Europe have been applying the principles of patent law to allow patents on microorganisms, plants and animals, the state of the IP law governing biotechnology remains unclear (Table 6.1). The United States and Europe have been faced with controversial issues, either in the application of the law itself or in the implementation of policy decisions intended to adapt patent law to this new, important technology. One important controversy concerns the extension of patents to genetic material and lifeforms, including cell lines, plants, animals and human body parts. Other concerns have focused on issues pertaining to the scope of the patent protection granted to biotechnological material and to economic issues such as exemptions for researchers and farmers. Neither governments, the courts, nor the patent offices have been able to settle completely the legal uncertainty surrounding the protection of biotechnological inventions.

Both the United States and Europe have been attempting to address the uncertainty in IP protection of lifeforms by leading efforts to protect lifeforms internationally [General Agreement on Tariffs and Trade–Trade-Related Intellectual Property (GATT-TRIP), WIPO and UPOV] and through their own legislative initiatives (Table 6.2). Although there has been some success at the international level, their own legislative actions have had little success. The social, economic, legal and ethical dimensions of these issues have prevented the U.S. Congress and the European Parliament from drafting and ratifying legislation that

satisfies both industry and broader public interests.

Table 6.2

Current Legislative Initiatives

United States	Europe	Canada
A bill to amend title 35, United States Code, with respect to patents on biotechnological processes, H.R. 587, 104th Cong., referred to Subcommittee on Courts and Intellectual Property. *An Act to Amend the Plant Variety Protection Act*, H.R. 2927, approved by the House Agriculture Subcommittee on Department Operations and Nutrition, on July 27, 1994. *Process Patent Act*, H.R. 4307, introduced by Rep. W. Hughes, Chairman of the House Judiciary Subcommittee on Intellectual Property and Judicial Administration, on April 28, 1994. *Transgenic Animal Patent Reform Act*, H.R. 4970, 100th Cong., 2d Sess. (1988), reintroduced H.R. 1556, 101st Cong., 1st Sess. (1989).	**Legal protection of biotechnological inventions:** Common position rejected in final vote of the European Parliament on March 1, 1995 after an unsuccessful codecision procedure. **Supplementary protection certificate for pharmaceutical products:** July 2, 1992, OJ 1992 L182/1. **Council Regulation (EEC) on Community Plant Variety Rights:** 2100/94 OJ 1994 L227/1, in force from September 1, 1994.	Drafting of the regulations implementing the *Intellectual Property Law Improvement Act*, S.C. 1993, c. 15, s. 38.1, allowing deposit of biological materials to supplement disclosure requirements.

Source: Research compiled by staff in the Intellectual Property Policy Directorate, Industry Canada..

The first major critical investigation of the international patent protection available for biotechnology was published in 1985 by the Organization for Economic Co-operation and Development (OECD). As part of an extended survey of the industrial and social impact of biotechnology, the OECD examined patent law and made positive recommendations for reform. At the same time, WIPO's Committee of Experts on Biotechnological Inventions published "suggested solutions" to the problems of patent law in this field.

In October 1988, the European Commission (EC) entered the arena with a proposal for a directive on biotechnology patenting which would solve these technical problems and provide a uniform approach throughout the Union. Over the last seven years, this directive has received significant scrutiny and undergone major revision. A compromise version in the form of a framework for patenting genetically altered organisms and other biotechnological inventions, developed over the last year, was decisively rejected by the

European Parliament in March 1995.[210] As a result, the patchwork of national patent rules across EU countries is still in place.

The following discussion summarizes some of the more significant articles of the directive as originally proposed in order to discern the thinking of its drafters, the EC.

Patentability of Living Matter

According to article 2 of the EU directive, an invention was not to be refused protection solely because it involved living matter. Although widely accepted, this principle needed restating to remove traces of past prejudices. It was amended to apply to biological material (i.e., any self-replicating living matter and any matter capable of being replicated through a biological system or by any indirect means), subject to certain exceptions in the EPC concerning plant and animal varieties.

Articles 8 and 9 were positive on the "product of nature" problem and declared that the mere pre-existence of a product, as part of a natural material, did not preclude its patentability.

Scope of Protection

This was addressed in articles 10 to 13. The scope of a patent for a biologically replicable material must extend to all progeny produced by multiplication of parental material which retained the characteristics of the latter. Although obvious to the scientist, there were legal reasons to make this affirmation. There is a legal doctrine according to which the rights of the patent owner are "exhausted" after the patented product has been placed on the market (either by the patentee or with his or her consent). That is, once a product has been sold, the purchaser has an implied licence to use and resell the product free of a claim for infringement. The strict application of this to biological material might mean that the purchaser of a single small amount of product would be free to cultivate unlimited quantities of descendant material from it. Articles 11 and 12 were designed to avoid this interpretation of the doctrine of "exhaustion of rights."

Article 10 was concerned with the question of experimental use of a patented product or process. It is generally accepted law that anyone may use a patented invention for experimental purposes. Thus, to use the invention for purposes of scientific enquiry or for evaluation is clearly permitted. It must also be possible for someone to experiment to find "ways around" a patent. The area becomes slightly grey if the experiment is carried out by an industrial competitor whose purpose is to improve or develop the invention and to commercialize the results. When living matter is involved and the developed product is a mutated or otherwise modified version of the original, this might be outside the scope of the

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[210] Betts, M.T. "Memorandum on EU Biotech Patenting - EurParl Rejects." Mission of Canada to the European Union, Brussels, Belgium, March 2, 1995.

patent. Once the new product has been produced, it will be possible to supply all future demand by replication of the developed product. Article 10 sought to remove the experimental use defence in these circumstances. This was undoubtedly a controversial proposal on which it was difficult to find a fair balance of interests.

Deposit of Biological Material

Articles 15 and 16 dealt with the deposit of microorganisms in culture collections. Those provisions sought not only to consolidate in national laws the whole complex of regulations found in the EPC and the Budapest Treaty, but also to extend them in a way that was more favourable to the patent applicant. This topic is examined more fully in Section 6.1.7.

6.1.5 Compulsory Licensing in Canada

Canadian patent law has given special treatment to pharmaceutical patents since the *Patent Act* of 1923. It permitted the Commissioner of Patents to grant compulsory licences (CLs) for the use of a patented process to manufacture medicines in Canada. The intention was to encourage multiple companies to manufacture the same drug thereby inducing competitive pricing. However, the legislation was largely unsuccessful with only 22 compulsory licences granted from 1923 to 1969. Suggested reasons for this result included the Act's requirement that active ingredients used in the manufacture of generic drugs be produced in Canada, the lack of profitability in manufacturing investments aimed exclusively at the small Canadian market and the dearth of patented medicines before World War II with profit potential.[211]

During the 1960s, three successive government studies (Restrictive Trade Practices Commission in 1962, the Royal Commission on Health Services in 1964 and the Harley Committee in 1965) concluded that drug prices in Canada were too high relative to production costs and compared to prices in other industrialized nations. The major underlying reason was deemed to be the then 17-year monopoly provided for Canadian patents. In response, the government, in 1969, passed *Patent Act* amendments allowing for the issuance of CLs to import patented medicines (or their active ingredients). As a result, from 1969 to 1987, generic companies filed 765 applications and received some 400 licences nearly all of which were licences to import.[212]

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[211] Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review.* Vol.10, September 1993, p. 145.

[212] Hill, E. and J. Steinberg. "Bill C-22 and Compulsory Licensing of Pharmaceutical Patents." *Canadian Intellectual Property Review.* Vol. 4, 1987, p. 44.

Under this statutory regime, controversy arose. The pharmaceutical industry argued that the statutory rationale for the compulsory licensing system had not, in practice, been fulfilled.[213] The Commissioner of Patents appeared to grant non-exclusive licences as a matter of right, on demand, and at a fixed royalty rate of 4 percent of the net selling price of the drug in final dosage form. In addition, provincial drug plans (aimed at the elderly and indigent) emerged in the 1970s, and encouraged substitution with the lowest cost equivalent of the prescribed drug. As a result, there was a readily accessible market for compulsorily licensed generic drugs. The rise of the generic drug industry during this period was considered by some to be a factor in the closure of R&D laboratories and the loss of related employment. The introduction of major tax incentives in the United States in 1981 and the somewhat hostile attitude toward the pharmaceutical industry in Canada have been mentioned as two reasons that worked against multinational firm expansion in Canada.[214]

The government responded by creating the Commission of Inquiry on the Pharmaceutical Industry (the Eastman Commission). The Commission concluded that savings due to compulsory licensing were significant, that multinationals had lost only 3.1 percent of the Canadian market due to generic competition by 1983, and that the government should not endeavour to make Canada a world centre for basic pharmaceutical research, but should direct activities toward clinical research where it had a comparative advantage.[215] Before the Eastman proposals could be fully considered for statutory enactment, the free trade negotiations with the United States intervened. In an environment influenced by American as well as domestic political forces, the Canadian government passed Bill C-22 (now S.C. 1987, c. 41) to amend the *Patent Act*, and in December 1987 provisions amending the compulsory licensing systems came into effect.[216] The purpose of the amendments was to encourage more multinational drug company R&D investments, to stimulate the manufacture of medicines in Canada and to maintain control over the prices of newly developed medicines through a price review board. These goals were pursued through the introduction of a period of market exclusivity prior to CLs being granted and the establishment of the federal Patented Medicine Prices Review Board (PMPRB).

In essence, under Bill C-22 compulsory licensing rights to import new medicines not invented or developed in Canada were deferred for 10 years from the date of the first notice of compliance (NOC) for the patented medicine, subject to certain transitional provisions

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[213] Before the 1985 consolidation of the *Patent Act*, section 39(4) and (5) were combined under section 41(4), the relevant portion of which read as follows: "in settling the terms of the licence and fixing the amount of royalty or other consideration payable, the Commissioner shall have regard to the desirability of making the medicine available to the public at the lowest possible price consistent with giving to the patentee due reward for the research leading to the invention."

[214] Manson, A.J. "The Impact of Compulsory Licensing on Pharmaceutical Research." *Canadian Intellectual Property Review*. Vol. 1, 1984, pp.164-169.

[215] *Report of the Commission of Inquiry on the Pharmaceutical Industry.* Minister of Supply and Services Canada, Ottawa, Canada, 1985. Cat. No. CP32-46/1985E. ISBN 0-660-11835-1.

[216] Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review*. Vol.10, September 1993, p. 145.

reducing the 10-year term to seven or eight years depending on whether the generic drug company had already received a licence or an NOC, but not both.[217] Compulsory licences for the manufacture of such patented medicines were deferred for seven years from the date of the patentee's first NOC. However, if the patented medicine was invented and developed in Canada, then a CL could only be authorized for the manufacture of such a medicine; no compulsory licence could ever be granted for its importation.

The period of exclusivity terminated after the earlier of either the expiry of the first patent on the medicine in question or the lapsing of the exclusivity period. The effect of the CL deferral system was to preclude generic products from entering the market for seven to 10 years after the patented medicine had received government approval. However, it was also an important step in reducing the discrimination against patented medicines which, unlike other inventions, were denied the full 20- year term of patent exclusivity as a result of compulsory licensing.[218]

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[217] Ibid

[218] In the Preliminary Comment on New Sections 39.1 to 39.26 [contained in *Patent Act* Chapter P-4 RSC 1985 and Amendments of Chapter 33 (3rd Supp.)], it is noted that "the provisions are labyrinthine in their complexity." In relation to CL deferrals, the Comments state that:

> [T]here are no deferrals whatever in relation to: a) patented drugs in relation to which there was at least one Section 39 licensee who had a NOC for the product as of 27 June 1986 (when the government's proposals for this legislation were first published); b) for importation or manufacture in Canada for export except in the case of patent on drugs having Section 39.16 status as described below.
>
> The deferrals themselves may be 7, 8 or 10 years, or even indefinitely in the case of section 39.16 status patents, depending on one or more of the following circumstances:
> (i) When and to whom the first NOC on the drug was issued;
> (ii) Whether the licensee proposes to import or manufacture the drug in Canada; and
> (iii) Whether there is an earlier, expired patent on the drug in question.
> ...
> Section 49.11(1) is the basic deferral provision so far as concerns exercise of section 39 compulsory licenses to *import*. It reaches both product and process patents where they are granted in respect of an invention pertaining to a medicine but only in relation to such medicine "for sale for consumption in Canada". Subsection 39.11(2) sets out the periods of time for which the deferrals specified in the previous subsection will apply. Where the first NOC for a drug was issued on or before 27 June 1986, the deferral will be until seven years after the date of such NOC if, as of 27 June 1986, there was either a section 39 compulsory licensee for the drug who did not have a NOC for it, or someone other than the patentee who, although having a NOC for the drug, did not have such a section 39 license. Note in this connection the extended definition of "patentee"in 39.1(1). The deferral will be eight years after the date of issue of the first NOC for the drug in question where, on or prior to 27 June 1986, only the patentee had a NOC, and no section 39 license had been issued. The deferral will be 10 years after the date of issue of the first NOC for the drug in question where such is granted after 27 June 1986. The prohibition against exercise of section 39 license rights of subsection (1) does not apply after expiration of the first patent granted in Canada in respect of the drug in question. It would seem that the expiration of a Canadian patent relating to a process for making such drug would not have the same effect.

The second major revision to the *Patent Act* under Bill C-22 was the establishment of the PMPRB. Its role was twofold:

- to review the prices of patented medicines to ensure that they are not excessive; and
- to collect information from patentees concerning their revenues from sales of medicines and their R&D expenditures (thereby monitoring the pharmaceutical industry's commitment to Canadian R&D investment).

The Board could also require third parties to submit information on the pricing activities of a pharmaceutical patent holder. To carry out its mandate, the PMPRB was granted certain statutory powers. If a patentee failed to provide required information or was found to be excessive in its pricing of a pharmaceutical product, the Board could:

- direct the patentee to lower the price; or
- revoke its compulsory licensing deferral in respect of the medicine in question; or
- *in extremis* revoke the deferral respecting any other patent of the patentee pertaining to any other medicine.[219]

Transitional provisions in Bill C-22 allowed for a review of the compulsory licensing deferral system and the PMPRB by the Governor in Council (i.e., the Cabinet) four years after certain of the amendments came into force (i.e., after December 7, 1991). It also required a comprehensive review by a parliamentary committee after nine years (i.e., after December 7, 1996). The reviews were intended, *inter alia*, to ensure that the pharmaceutical industry would live up to its commitments to increase its Canadian R&D expenditures.[220] As a result, the provisions according extended patent protection could be repealed or modified, depending on the industry's performance.

Despite these far-reaching 1987 amendments, controversy continued, and the government announced its intention, in January 1992, to abolish all compulsory licensing of medicines in Canada in accordance with its expected obligations under the GATT. On December 20, 1991, Mr. Arthur Dunkel, Director General of the GATT, tabled the Draft Final Act Embodying the Results of the Uruguay Round of Multilateral Trade Negotiations (the Dunkel Draft). Its provisions pertaining to TRIP agreements required that 20-year patent protection be available for inventions (except exempted subject matter) whether of products

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Licensees who had both a section 39 license and a NOC for the drug in question as of 27 June 1986 are by 39.11(4) "grandfathered", and it appears from the wording of this provision that such immunity from the deferrals of subsection (1) is not limited to the particular licensee in question, but can be taken advantage of by other licensees.

219 Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review*. Vol.10, September 1993, p. 145.

220 *Ibid*

or processes, in all fields of technology.[221] Canada's compulsory licensing system was, in effect, contrary to the Dunkel text. The federal government endorsed the text of the Uruguay Round of GATT and, in so doing, signalled its willingness to repeal the compulsory licensing scheme in Canada. Bill C-91 (now S.C. 1993, c. 2) was introduced in June 1992 before the House of Commons.

The North American Free Trade Agreement (NAFTA) announced on August 12, 1992 by Canada, United States and Mexico, was another factor in the government's introduction of Bill C-91. NAFTA expanded the earlier Canada–United States Free Trade Agreement by including provisions on intellectual property rights. Articles 1703 and 1709 of NAFTA were of particular importance in relation to the C-91 amendments. Under article 1703, the treatment each country accords to nationals of another country can be no less favourable than it accords to its own nationals with regard to the protection and enforcement of all IP rights (a similar provision is in GATT). As a result, Canada was required to treat inventions of medicines researched and developed off-shore the same as those researched and developed in Canada. In practice, this meant that for U.S. patents, research done in Canada or Mexico would now be on an equal footing with research done in the United States and, presumably, the United States would have to treat inventions produced in Canada the same as those produced in the United States.

Article 1709 required each country to make available patents for inventions, whether products or processes, in all fields of technology provided that such inventions are new, result from an inventive step and are capable of industrial application (i.e., the invention must be new, useful and non-obvious). This reaffirmed the existing criteria for granting a patent in Canada, much of which was enacted under the non-pharmaceutical-related amendments to the *Patent Act* in 1987. Under paragraph 7 of article 1709, patents are to be made available and patent rights enjoyed without discrimination as to the field of technology, the territory where the invention was made and whether the products are imported or locally produced. With the repeal of the compulsory licensing provisions by Bill C-91, medicines were treated the same as any other patented product in terms of length of exclusive patent protection.

Paragraph 12 of article 1709 requires each country to provide a term of protection for patents of at least 20 years from the date of filing. A country may extend the term of patent protection to compensate for delays caused by regulatory approval processes. This paragraph was inserted primarily to allow the United States to keep its own current patent term restoration legislation. Nothing before or after NAFTA prohibits Canada from adopting similar patent term restoration provisions in its *Patent Act*.

The *Patent Act* has recently been revised twice to implement Canada's international obligations arising from the NAFTA (Bill C-115, now S.C. 1993, c. 44 in force on January 1, 1994) and the GATT–TRIP agreements (Bill C-57, now S.C. 1994, c. 47 in force on January 1, 1996). There is considerable overlap in this area between NAFTA obligations and those flowing from the TRIP agreements. Once modified to comply with NAFTA, the

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221 *GATT Activities 1991, An Annual Review of the Work of the GATT*. Geneva: GATT, 1992.

Patent Act basically complied with the GATT–TRIP agreements as well. Although none of the amendments made to the *Patent Act* on these two occasions dealt specifically with pharmaceutical or biotechnological inventions, the modifications adopted under the *NAFTA Implementation Act* have introduced a mechanism for government use of a patented invention without the right holder's authorization. It also provides for a reversal of the burden of proof for patented processes in infringement cases.

Under Bill C-115, the Commissioner of Patents may authorize the use of a patented invention by the Government of Canada, or the government of a province. Although such use has been restricted in duration and is limited to supplying the domestic market, it still allows the government to interfere with the patent protection afforded to products or processes. Once an applicant establishes that it has made efforts to obtain, from the patentee on reasonable commercial terms and conditions, the authority to use the patented invention and that such efforts have not been successful within a reasonable period, it would appear that either the federal or the provincial government could obtain a CL to import, make or sell patented medicines, notwithstanding the fact that Bill C-91 has abolished the compulsory licensing system in Canada. In view of the provincial governments' increasing exposure to drug costs, this provision of Bill C-115 would confer an additional means of controlling the price of pharmaceuticals. Shifting compulsory licensing from the hands of generic companies into the hands of the government allows the government to offer generic copies of brand name drugs and changes the dynamics of the competitive marketplace by adding a third-party supplier.[222]

Proponents of Bill C-91 have argued that it is progressive legislation since it brings Canada's pharmaceutical patent protection into line with other industrialized countries. The federal government has declared that this legislation fulfils several important objectives.

- It modernizes Canadian IP legislation as part of the task of improving Canadian competitiveness.
- It stimulates R&D, economic growth and investment in the pharmaceutical sector.
- It strengthens consumer protection and provides Canadians with patented medicines at reasonable prices.

To attain these objectives, Bill C-91 amendments abolished compulsory licensing for pharmaceuticals and restored to the patentee the exclusive right to make, use and sell its patented medicines for 20 years from the application date. This added, on average, three years of market exclusivity for patented pharmaceutical products. It also meant that generic drug companies would no longer be able to obtain CLs to make, use or import patented medicines except in very restricted cases. For instance, only CLs issued by the Commissioner of Patents before December 20, 1991 could continue to be used.

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[222] Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review*. Vol.10, September 1993, p. 145.

The powers and sanctions of the PMPRB have been strengthened by giving it the authority to review prices of both new and existing patented medicines. The Board can order price reductions or penalties that compensate for past excessive prices and deter excessive pricing practices. The Board's orders have been given the same force and effect as an order of the Federal Court of Appeal. The Board's powers provide for fines (of up to $100,000/day for a company and $25,000 for an individual) and imprisonment for failure to comply with its orders.

Responsibility for the Board has been transferred to the Minister of Health. On the matter of appointments to the Board, the Minister is advised by a panel which includes representatives of the provincial ministers responsible for health, consumer groups, the pharmaceutical industry and such other persons as the Minister considers appropriate to appoint [section 92(1)]. The Minister may enter into agreement with any province respecting the distribution to that province of amounts received or collected by the Receiver General (section 103).

The C-91 amendments (contained in section 55.2) enable the Governor in Council to prescribe regulations establishing a link between the health and safety approval of a product and the patent status of the product. These amendments allow a manufacturer to make use of a patentee's inventions to stockpile products for sale after expiry of the patent. They clarify that the use of patented inventions for experimental purposes and for obtaining regulatory approval, including obtaining an NOC from Health Canada, do not constitute infringement of patent rights. All these provisions and regulations came into force March 12, 1993.

As well, the amendments provide for a referral to a parliamentary committee. This is to take place four years after royal assent (i.e., February 1997), on the expiration of the provisions of the *Patent Act* enacted by Bill C-91.

Critics of Bill C-91 argue that its timing and retroactive effect were unfair and contrary to Parliament's intentions regarding Canadian pharmaceutical policy as expressed in Bill C-22 in 1987. The four and nine-year reviews built into the C-22 amendments were intended to provide the Canadian pharmaceutical industry with needed time to react to, and adjust to, the extended periods of pharmaceutical patent protection provided in those amendments. Also, there appeared to be undue haste to ratify Bill C-91 before either the GATT or NAFTA had been ratified.

Furthermore, the U.S. federal government was showing an interest in controlling its own drug costs. The U.S. General Accounting Office conducted a study into the prices of brand name prescription medicines and found that U.S. costs were 32 percent higher on average than in Canada. That study noted that "government policies in Canada were the major reason for the price gap" and mentioned the PMPRB and provincial drug plans "which insist on the lowest possible price before agreeing to compensate patients for a particular drug." It also noted that Canadian pharmaceutical patent legislation (before C-91) "which allows generic products on the market to compete with brand name drugs much earlier than in the

United States" probably contributed to the lower prices of drugs in Canada.[223]

In summary, Bill C-91 has both advantages and disadvantages.[224] The advantages include:

- the harmonization of Canada's pharmaceutical patent legislation with that of other industrialized countries;
- encouraging prospects of world product mandates for Canada;
- channelling additional revenue for R&D in Canada; and
- granting increased powers to the PMPRB to ensure continued consumer protection.

The disadvantages include:

- the absence of effective controls on non-patented medicines (full patent protection is "locked-in" under NAFTA by pre-empting the review required by Bill C-22);

- the absence of a statutory guarantee of increased R&D spending by brand name pharmaceutical companies leaving the R&D spending levels to their discretion; and

- the absence of leverage over total costs to the Canadian public.

A checklist[225] for monitoring the effectiveness of Bill C-91 in the future would, therefore, include:

- the prices of medicines in general in Canada;

- the ability of the PMPRB to control effectively patented medicine prices in Canada;

- private insurers and whether they will pressure physicians to prescribe generic medicines rather than brand name medicines;

- brand name drug companies and whether they will continue to attempt to persuade physicians to specify "no substitution" on prescription forms;

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223 Mickleburgh, R. "Prescription drugs cheaper in Canada, report finds." *The Globe and Mail*, October 22, 1993, p. A10.

224 Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review*. Vol.10, September 1993, p. 145.

225 Ibid

- the increase in R&D expenditures by pharmaceutical companies in Canada (and the public benefits accruing therefrom); and

- the number of patents dedicated to the public in an attempt to avoid the PMPRB's jurisdiction after market share for the medicines has been established.

Finally, we note an argument, reported by Horton of C-91 opponents[226] that Canada, as a heavy net importer of technology, has "sharply different interests in the patent system" than countries, such as the United States, which are major exporters of technology.

6.1.6 Higher Lifeforms

The recently rejected EU directive on biotechnology inventions addressed the issue of the patentability of higher lifeforms. It is useful to explain European law regarding agricultural inventions and how it differs from U.S. law.[227]

Plant and animal varieties are unpatentable under European patent law. To be patentable under European patent law and the harmonized national laws of most European countries, an invention must be capable of industrial application. Agriculture is treated the same as any other industry by the EPC. However, the EPC specifically excludes patents for certain innovations related to plants and animals as described below. Patents are obtainable for a wide range of agricultural and horticultural methods and products, subject to the usual requirements for novelty and an inventive step which apply generally to inventions in all fields. Thus, biological agents to control agricultural pests and weeds are in the product patent category, novel plant micropropagation techniques can be protected as method or process patents, and the application of plant-cell and tissue-culture methods to prepare useful metabolites are in the patentable process technology area. Certain exclusions exist in the EPC stemming from older legal policies laid down before the impact of second generation biotechnology on agriculture was foreseen. These exclusions also exist in the patent laws of other important countries with major exceptions, notably in the laws of the United States and Japan.[228]

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226 Ibid

227 Greengrass, B. "The 1991 Act of the UPOV Convention." *European Intellectual Property Review*, Vol. 12, 1991, pp. 466-472.

228 Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp.151-157.

In the *Chakrabarty* case,[229] the U.S. Supreme Court upheld a patent for a genetically manipulated bacterium on the ground that it was "a non-naturally occurring manufacture or composition of matter, a product of human ingenuity." The Court stated that patents can be allowed for "anything under the sun that is made by man." This statement justified the allowance of patents for organisms higher than bacteria and provided confirmation that patents can also be obtained for plants which meet this criterion.[230]

In due course, the U.S. Patent and Trademark Office (USPTO) Board of Patent Appeals and Interferences held that plants, i.e., the Hibberd patent (corn plants, seeds and plant tissue culture), were patentable subject matter. Under U.S. law, the same plant can, in some circumstances, be protected by a patent granted by the USPTO as well as by a certificate of variety protection issued by the Department of Agriculture under the *Plant Variety Protection Act* of 1970.

To obtain a patent, the plant must embody an invention whereas, for the certificate, the ordinary tests for new varieties apply.[231] The Hibberd case and another one [*Ex parte Allen* 2 USPQ (2d) 1475] were followed by the general statement of the U.S. Commissioner of Patents that "the Patent and Trademark Office now considers non-naturally occurring non-human multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 USC 101."

In conformity with this policy, the first U.S. patent for a transgenic animal was issued to the president and fellows of Harvard College. This is popularly known as the Harvard oncomouse patent although its claims are not limited to the mouse and broadly cover "a transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage."

The current official position in the United States appears to be stable with regards to patents for novel types of plant and animal, so long as patentability criteria are met.[232]

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229 *Diamond vs. Chakrabarty*. U.S. patent case. *United States Patent Quarterly*. 206, 193, 1980.

230 Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp.151-157.

231 During the 1920s and 1930s, it became widely recognized that systematic plant breeding was of benefit to society and that there was no effective protection system. Initially, plant breeders sought protection under the patent system, but a number of technical difficulties were encountered in seeking to apply the patent system, designed to protect inanimate inventions, to plant varieties, which were thought not to reproduce themselves precisely, and whose appearance could vary depending on the environment in which they were grown. Therefore, a number of countries passed separate legislation in the nature of variety protection rights, which were completely separate from the exclusive rights protected by the patent laws.

232 Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp.151-157.

Although the question of patents for plants and animals has been controversial, Japanese patent law does not preclude such patents, and some have been issued. Japan also has a "seeds and seedlings" law, and plants may be protected under either this law or the patent law (or both in appropriate cases). When the plant is a new variety, bred by classical plant breeding methods, it would be difficult to obtain a patent for it. Japan has granted some patents for animals usually defined as products of a particular method.[233]

In contrast to U.S. and Japanese laws, European patent laws contain a number of specific exclusions, among which is the exclusion of patents for "plant and animal varieties and essentially biological processes for the production of plants and animals." Article 53(b) of the EPC, the normative patent statute for most of Western Europe, is the provision around which controversy exists. The origin and purpose of the prohibition of patents for plant varieties stems from the early policy of traditional plant breeders and the agricultural industry in Europe to operate a system of legal protection of narrower scope and, therefore, one that was less strong than if patents were allowed. Hence, a parallel system of legal protection for plant varieties (known as plant breeders' rights or plant variety rights) arose under national laws and the UPOV Convention. The UPOV Convention allowed member states to grant either patents or plant variety rights for the same entities, but prohibited the granting of both types of protection simultaneously (now referred to as cumulative protection). This form of protection is weaker than that of patents because the rights are, to a great extent, limited to the commercialization of the reproductive material of the specific variety (seed or vegetative). Also, the farmers and breeders are allowed certain freedoms (i.e., the farmer's privilege and the breeder's privilege or the research exemption mentioned in Section 6.1 of this chapter). These laws are currently under review.[234]

In relation to plant varieties, the EPC legislators went a stage further than UPOV and deliberately excluded patents for plant varieties in article 53(b). This has led to confusion since in the absence of a clear definition of the term "variety" and uncertainty over the term "essentially biological," the meaning and scope of the exclusion could only be determined by judicial authority or by further clarifying statute law. Article 53(b) adds to the difficulty by stating that the exclusion does not apply to "microbiological processes and the products thereof."[235]

Since genetic manipulation (e.g., by recombinant methods) will produce new "types" of plant material which are not yet developed to the stage of the variety, but which form the parental material from which varieties will eventually be bred, the straightforward view would be that, since these plants incorporate an invention, they should be patentable. However, under the present EPC, patentability depends entirely on the wording of the patent claim and on how it is construed, i.e., whether the claim is directed to a finished variety as such, or to some other level of classification which cannot be refused under the

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233 Ibid

234 Ibid

235 Ibid

particular article.[236]

Plant products of traditional breeding (hybridization, cross-pollination, backcrossing and selective breeding) do not fit easily into the criteria of patentability. It is difficult to apply the concept of the inventive step to a plant variety, but the main problem is to describe a method of producing a particular variety that can be repeated. There are few examples, therefore, of attempts to patent plant varieties of the typical kind for which plant variety rights are granted. This tends to give this debate an academic rather than a practical character.[237] The rejection by the Supreme Court of Canada in the *Pioneer Hi-Bred* case [Pioneer Hi-Bred 14 *Canadian Patent Reporter* (3d) 491] of a patent application for a soybean variety, produced through cross-breeding and selection, provides a model of the type of patent claim that would be presented for a variety obtained in this way. The application was rejected because it did not contain sufficient disclosure since the depositing of samples of seeds of the new variety did not constitute disclosure within the meaning of section 34(1) of the *Patent Act*. Although seeds of the variety had been deposited with a culture collection, the Court did not accept the deposit as a substitute for a description. In so deciding, the Canadian court was out of line with the courts of the United States, Europe and Japan.[238] This claim was based essentially on a listing of phenotypical properties, and it might be difficult in many cases to identify an inventive concept in any one such property or in any combination. This concrete example may help in the future to clarify the issues in discussions between patent and UPOV circles which have often been at cross-purposes for want of agreement over terminology.[239] Readers should note, however, that a recent amendment to the *Patent Act* (yet to come into force) allows deposits of biological material to complete the disclosure requirements under the Act.

The draft EU directive, previously discussed, attempted to steer a course which remained true to the EPC while being more positive with regards to the extent of patentability outside the restrictions of EPC article 53(b). Accepting, therefore, that patents are not granted for plant varieties, as such, the last sentence of article 3 of the draft directive stated: "Claims for classifications higher than varieties shall not be affected by any rights granted in respect of plant and animal varieties." Thus, the possibility of patent protection for plant-related inventions, capable of application to particular varieties, would have been confirmed. If this affirmation, or some equivalent statement, were supported by member states it would have strengthened the patent protection available in agricultural biotechnology.

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236 Ibid

237 Ibid

238 Ibid

239 Ibid

Whether a patent that only has claims for deoxyribonucleic acid (DNA) sequences can protect their expression products (i.e., proteins) is a matter of dispute in U.S. law which arose in the Erythropoietin (EPO) case between Amgen Inc. and Genetics Institute Inc.[240] The question of whether such DNA patents extend to plants transformed with the DNA should be easier to answer, since the DNA is still there in the resulting plant. Nevertheless it may not be sufficient for commercial purposes to rely on DNA patents alone (i.e., those which do not also claim the embodiment in plants). Biotechnology companies will want assurance that patents on the genetic material will not be infringed through a lack of their ability to enforce patent rights on the final marketed products.[241]

Animal patents in the United States and Japan are now granted even though there continues to be some opposition to granting animal patents. In Europe, the Harvard oncomouse product claim was rejected by the Examining Division (ED), but was sent back by the appeal board for reconsideration. The ED, in reconsidering the application, held that claims directed to non-human mammals and rodents, animals per se, did not fall within the scope of the terms "animal variety," "race animale" or "tierart" as found in article 53(b) of the EPC. It also held that the Harvard oncomouse patent did not offend "ordre public" under article 53(a). The patent was then issued and was later subject to formal oppositions. It is likely that a decision on the oppositions will be reached in late 1995.

Animal genetic manipulation is considered by some to be an ethical question but this point was not formally relied on by the ED even though EPC article 53(a) forbids patents for inventions which, if exploited, would be contrary to public morality. This is another point which the appeal board asked the ED to reconsider. While official patent circles and the industries that use biotechnology in Europe have not questioned the appropriateness of intellectual property for new processes and products emerging from research involving higher lifeforms which show commercial promise, a highly vocal challenge to this assumption has come from the animal rights and environmental movements, and their supporters in the European political arena.

Taking a stand on what they believe is the unethical practice of "patenting life," the opposition by these groups extends to any significant structural change in the agricultural industry which might stem from biotechnology, and especially from control by established corporations of monopoly rights on research advances. This argument is applied to both plant and animal biotechnology and, in the latter case, a moral objection is also raised against interference with the assumed right to integrity of the species. This opposition is targeted against the patenting of these inventions as well as against the research itself. The opposers have clearly appreciated the role of patent protection in stimulating the funding of this research, and their strategy is clear. This movement is highly active in the United States and in the European parliamentary system and can be expected to maintain a high

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[240] Crespi, R.S. "Biotechnology and Intellectual Property. Part 1: Patenting in Biotechnology." *Trends in Biotechnology*, Vol. 9, April 1991, pp.117-122

[241] Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp.151-157.

profile in public debate for some time to come.[242]

6.1.7 Culture Collections

It is a fundamental requirement of patent law that, in return for legal protection, an inventor must disclose the invention in a manner sufficiently clear and complete to enable others of ordinary skill in the art to repeat or reproduce the process or product for which the patent is granted). When the invention consists of, or depends on, a specific microorganism or other kind of biological material, the material must be identified in the patent application to fulfil the required enabling disclosure.

When the microorganism is known and already available to the skilled person, and the invention resides, for example, in the discovery of some new property or use of practical value, it is usually sufficient to refer to the microorganism by name. For a new microorganism (e.g., a newly isolated or developed strain of a known species), the skilled person who attempts to repeat the procedures described in the patent specification will, in most cases, need not only a description of the organism but also a means of access to it. Now if the patent application gives reliable instructions for re-isolating, rediscovering or reconstructing the new organism, this will be a sufficient disclosure. However, in most cases this cannot be achieved with certainty. Patent law has solved this problem by making use of the culture collection deposit system which the scientific community had created much earlier for its own needs. The applicant deposits a sample of the material with an officially approved culture collection which is equipped to store and handle it and then files the patent application giving details of the deposit.

The deposit of the organism supplements the written description. It also fulfils other important functions.

1. It provides a reference material for resolving any dispute over the alleged novelty of the organism.

2. Its reference function may be called on to decide whether any third party is infringing the patent by using the same organism without a licence from the patentee.

3. The deposit provides an available source material to enable others to make use of it when they are legally free to do so (i.e., when the patent has been issued or the application is finally refused, abandoned and no longer subject to reinstatement, or withdrawn).

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242 Ibid

The practice of depositing microorganisms in culture collections for patent purposes has developed internationally both through case law and in the express obligations written into modern patent laws in many countries. The maxim that what cannot be described fully must be deposited has become fixed in patent law either by court decisions or by statute. This development has added a new dimension to patent law and practice for which no parallel exists in other fields of technological innovation.[243]

When an applicant decides to seek patent protection, the application filed at the patent office is held secret in the early stages. While this secrecy holds, an applicant should try to assess the chances of success in gaining effective legal control of the invented item of technology, a prospect which depends crucially on the quantity, quality and originality of the data generated by the research team. The reason for this advice is that under modern patent law the secrecy of the patent application lasts only a short time. In many countries (including Canada), the application must be published 18 months from the date of its filing. The applicant is then exposed to whatever advantages this disclosure will give to competitors in the following period before the prosecution of the case is complete and his or her rights are determined. The major policy decision to live with these consequences must have been taken by this time because publication cannot be stopped unless the patent application is withdrawn in good time beforehand. As a result of publishing the patent application, the deposited biological material must also become available to the public along with the written text of the publication.

There is a difference between U.S. and Japanese patent systems, on the one hand, which allow access to the deposited culture only after an enforceable right has been granted to the applicant and, on the other hand, the corresponding laws in European countries which allow access to the deposited culture on first publication of the European or national patent application.

Both the EPC and the separate national patent laws in most European countries have rules which provide for access to deposited cultures at this early publication stage. Rule 28 of the EPC is the prototype regulation dealing with deposit and release of microorganisms. At this early stage, the application has not yet been officially examined and no effective right has been obtained (i.e., the applicant is still only an applicant and not yet a patentee). The drawbacks of the European law have been emphasized by industry from the very beginnings of the EPC itself (which began operation in 1978), and efforts to improve the law have continued unabated since then (see Table 6.3).

The compulsory release of deposited cultures at the early publication stage is the greatest single disincentive to the use of the patent system for the protection of microbiological inventions.[244] The easy availability of the valuable new microorganism to third parties without geographical limitation has significant consequences:

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243 Ibid

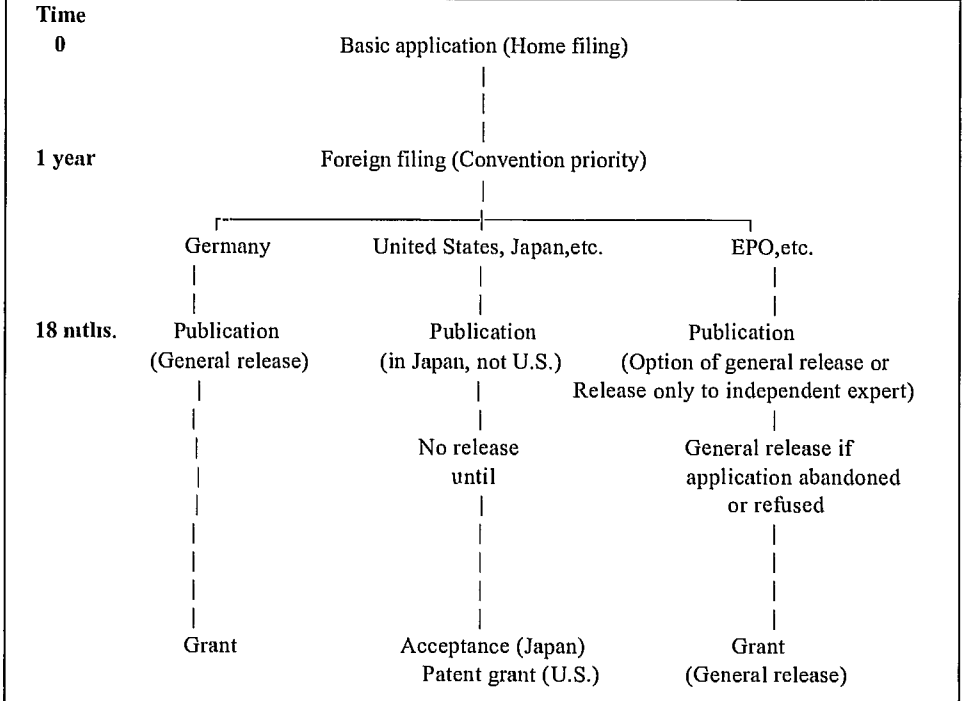
244 Ibid

- the immediate loss of any effective control of the microorganism and its uses;
- irrevocable loss of any option for the applicant to revert to trade secrecy if the prospects of patent protection are not encouraging; and
- the immediate vulnerability of the applicant to genetic modification of the microorganism and the circumvention of the protection.

Loss of control of the new strain, at least for competitive research purposes, is mitigated under European patent practice by the option to elect for the so-called "independent expert" solution in the interim period between publication of the application and eventual grant of the patent. Under the EPC, this concession (operating since June 1980) allows for availability at the early publication stage to be restricted to an independent expert acting for the third party. The expert is able to experiment with a sample of the deposit and to communicate the results, but must hold the sample on trust. In this way the proprietary material is kept out of the hands of competitors and others during the time that the applicant has no enforceable right.

Table 6.3

A Representation of the Comparative Practices of Some Countries in Regard to the Availability of Biological Samples Deposited in Culture Collections to Fulfil the Requirements of Patent Applications that Involve Newly Isolated or Modified Microorganisms



Source: Crespi, R.S. "Biotechnology and Intellectual Property. Part 2: Microorganism deposit questions and agricultural biotechnology issues." *Trends in Biotechnology*, Vol. 9, April 1991, pp. 151-157.

The parties are expected to agree on an appropriate expert who has their confidence. When this is not possible, the parties can select one from an official list of scientists accepted by the European Patent Office (EPO) for this purpose. The EU has taken the view that something should be done to ameliorate the position of the applicant with regards to the operation of the deposit rules. There is, of course, a limit to what can be done because, after a patent has been granted, the deposit must be open to all comers as part of the patent disclosure.

Article 15 in the EU's directive of 1988 [an amended version of which was rejected by the European Parliament in March 1995 (see Section 6.1)] sought first to achieve uniform adoption of the expert solution in all national laws of member states. The article would have permitted the applicant to withdraw a deposit if the application was abandoned or a patent denied. (This part of the proposal was resisted strongly by the EPO on the grounds that once a deposit has become public it must remain so.) Article 15 also proposed to place an "experimental use only" restriction on samples released to persons in countries where no corresponding patent applications have been filed. On these last two points, article 15 was difficult for member states to accept, and other remedies were sought. Crespi notes that whatever was proposed for European countries, the U.S. Patent Office would not allow restrictions on availability of the deposit once the U.S. patent was granted.[245] There has been no move by U.S. industry to change this official view. Since it will be rare for a biotechnological invention of any significance *not* to require U.S. protection, the inevitable unrestricted access to a deposit made for U.S. purposes is a limiting factor for those who argue for tighter controls on availability elsewhere.[246]

6.2 Canadian Biotechnology Intellectual Property Statistics

6.2.1 Canadian Biotechnology Patent Statistics

In this section, we analyze summary statistics on biotechnology patents originating with the Canadian Intellectual Property Office (CIPO), Intellectual Property Policy Directorate (IPPD), U.S. Patent and Trademark Office (USPTO), and European Patent Office (EPO).

Table 6.4 shows the number of biotechnology patent applications filed with CIPO from 1985 to 1993. The number of applications peaked in 1989 (2,353 applications), and declined about 10 percent in 1990 (2,106 applications). After a slight recovery in 1991 of 3 percent (to 2,188 applications), the level fell 37 percent in 1992 and by another 31 percent through September 1993. The data indicate a recent significant decline in patent applications filed with CIPO for biotechnology inventions. Neither CIPO nor the IPPD could provide a reason for this decline.

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245 Ibid

246 Ibid

Table 6.4

Number of Biotechnology Patent Applications Filed with the CIPO: 1985-1993

Year	No
1985	1,192
1986	1,387
1987	1,598
1988	1,877
(Jan-Sept) 1989	1,906
(Oct-Dec) 1989	447
1990	2,106
1991	2,188
1992	1,323
(Jan-Sept) 1993	582
Oct/89-93 Total	**6,646**

Source: Data from October 1, 1989 through September 24, 1993 based on applications filed under the *Patent Act* with Bill C-22 amendments.

CIPO provided a data base to the IPPD of Patent Co-operation Treaty (PCT) "laid open" biotechnology patent applications (i.e., patent applications available to the public 18 months after the priority country date of filing) also filed in Canada. The data base also includes a sample of applications in patent classifications with claims to lifeforms which were filed in priority countries between October 1, 1989 and March 31, 1992 (tables 6.5 through 6.11). The data base consists of laid open biotechnology patent applications filed under the new act (i.e., the *Patent Act* with the 1987 Bill C-22 amendments).

Caution in the interpretation of the related statistics is warranted for several reasons.

1. Data on patent applications filed in other countries under the PCT may be received in Canada up to 30 months after the priority filing date. Hence, a PCT application filed in another country in December 1991 could have been received in Canada as late as June 1994. As a consequence, the IPPD data base of PCT patent applications filed in Canada is incomplete and is only a representative sample of biotech applications filed in Canada during this period.

2. The data base includes patent applications for which the applicant has not requested examination.

3. The data base includes about half of the biotechnology patent applications in CIPO filed under the new act.

4. The data base focuses on biotech patent applications with at least one claim on a lifeform. However, most of these applications also include claims to chemical compounds and processes. A significant proportion claim hybridomas. Therefore, it does not include all patent applications under CIPO's broader definition of biotechnology classifications.

Examples from the data base include:

- recombinant deoxyribonucleic acid (rDNA) technology relating to microorganisms, RNA, cells, plants, animals, etc.;
- gene therapy;
- medicinal preparation containing material proteins, antibodies, animals, plants, proteins, etc.;
- plant reproduction techniques (including tissue culture); and
- processes to purify existing compounds using enzymes and microorganisms, preparation of peptides, proteins, etc.

The data base contains information on the applicants, inventors, filing and laid open dates, type of patents (product, process, apparatus or a combination of these), and detailed claim information.

Table 6.5 shows the distribution of applications by applicant country and priority country. The priority country is the country of first filing.

- In the case of applicant countries, nearly half the applicants were American. The six countries with more applicants than Canada were the United States, 49 percent; Japan, 13 percent; Germany, 8 percent; United Kingdom, 6 percent; France, 5 percent; and Switzerland 4 percent. By comparison, Canadian applicants had 3 percent of all applications. On a per capita basis, Canadian inventors filing biotechnology patent applications with CIPO rank among the top five countries in biotechnology invention. However, these data overestimate the strength of the Canadian biotechnology sector since inventors tend to file more intensively in their home countries (see below).

- Of the biotechnology patents filed in Canada, 16 countries had more priority applications than Canada. In order, these were the United States, 54 percent; Japan, 13 percent; United Kingdom, 7 percent; Germany, 7 percent; France, 4 percent; Switzerland, 1.5 percent; Italy, 1.2 percent; Australia, 1 percent; Denmark, 0.9 percent, Austria, 0.8 percent, the Netherlands, 0.8 percent; Sweden, 0.5 percent, Israel, 0.5 percent; Norway, 0.4 percent; and Finland, 0.4 percent. By comparison, Canada had virtually none (two priority applications).

- Most applicants, particularly U.S., Japanese, German, U.K., French, Italian, Australian, Danish, Austrian, Swedish, Israeli and Norwegian applicants, were more likely to file first in their home country. The exceptions were inventors from Canada and the Netherlands.

- Multinational biotechnology firms usually file their patent applications first in their home country.[247]

Table 6.5

Number of Biotechnology Patent Applications Received in Canada According to the Applicant Country and the Priority Country: 1989-1992

Country	Applicant Country	Priority Country
United States	1,589	1,724
Japan	431	415
Germany	249	226
United Kingdom	184	240
France	147	131
Switzerland	140	48
Canada	101	2
Netherlands	80	25
Italy	52	40
Australia	36	34
Denmark	34	30
Belgium	31	NR
Austria	31	27
Sweden	22	17
Israel	21	16
Finland	21	12
Norway	14	14
Hungary	7	NR
China	5	NR
Soviet Union	4	NR
Ireland	4	NR
Liechtenstein	3	NR
Cuba	2	NR
Venezuela	2	NR
Republic of Korea	2	NR
Singapore	1	NR
Spain	1	NR
Taiwan	1	NR
Luxembourg	1	NR
Mexico	1	NR
Yugoslavia	1	NR
South Africa	1	NR
India	1	NR
Others		124
None		105
Total	**3,220**	**3,220**

Note: NR means not reported.
Source: IPPD patent data base of PCT laid open applications claiming lifeforms.

[247] Wyatt S., G. Bertin and K. Pavitt. "Patents and Multinational Corporations: Results from Questionnaires." *World Patent Information*, Vol. 7, 1985, p. 196.

Interviews provided some reasons for the tendency of Canadian applicants to file their applications first in the United States (see Global Patent Strategies). However, it should be clear from the discussion to date that the value of IP protection depends on the size of (and access to) the market in which that protection exists.

- The order of preference for biotechnology firms to protect their IP in important markets is the United States first, Europe second and Japan or Canada third.

- The data show that 96.9 percent of Canadian biotechnology patent applications come from foreign inventors (94 percent of North American applicants are from the United States). As a result, most Canadian practitioners prosecuting biotechnology patent applications in this country represent applicants residing in the United States, not in Canada.

These data suggest that strengthening biotechnology IP protection in this country may have significant economic impacts and could lead to an acceleration in the growth of Canada's biotechnology trade deficit.

- The top 10 biotechnology patent applicants in Canada together filed 530 applications, or 16.5 percent of the total (Table 6.6). Four of these applicants were from the United States, two respectively from Germany and Switzerland, and one each from Japan and the Netherlands.

Table 6.6
Leading Biotechnology Patent Applications in Canada: 1989-1992

Name of Applicant	Number of Applications
Merck & Co. (U.S.)	107
Takeda Chemical Industries Ltd. (Jpn)	59
Eli Lilly (U.S.)	55
U.S. Dept. of Commerce	53
Behring AG (Germany)	53
Ciba-Geigy (Switz.)	48
American Cyanamid Co. (U.S.)	44
Hoechst AG (Germany)	40
Hoffman-LaRoche (Switz.)	39
Akzo N.V. (the Netherlands)	32
All other applicants	2,690
Total	**3,220**

Source: IPPD patent data base of PCT laid open applications claiming lifeforms.

Although biotechnology patenting is not concentrated among a few firms, the profile of the leading biotechnology patent applicants further demonstrates the general domination of the United States, Japan and Europe in the filing of patent applications for biotechnology inventions in Canada.

- Canadians not only lag behind in the overall number of patent applications, but also in the number of patents filed per Canadian biotechnology applicant. A review of the 101 laid open Canadian biotechnology patent applications in the IPPD data base revealed that there were 80 different applicants.

The number of patent applications for plants and animals varies greatly among the United States, Europe and Canada (Table 6.7).

- The United States leads the way in patenting higher lifeforms, especially in animal applications, since there were 1.5 times more animal patent applications filed in the United States than in Europe and more than 10 times the number of applications as in Canada.

- While the United States leads the way in both plant and animal patent applications, the lead is narrower for plant applications. In the United States, the ratio of applications for plants as opposed to applications for animals was 1.6:1. This ratios was 2:1 for Europe and 4.3:1 for Canada. Note that these ratios have been amended to reflect the correct interpretation of EPO data on patents for plants per se and animals per se (see notes for Table 6.7).

- The United States has been fairly active in granting patents on plants (176) as has Europe (50 to 100). Canada has yet to grant a patent on a plant.

The picture is somewhat different for animal patents, since there have been only a few animal patents granted throughout these three regions. The United States leads with seven patents granted for animals. Europe has only granted one patent on the Harvard oncomouse, and Canada has yet to issue an animal patent.

Table 6.7

Number of Higher Lifeform Patent Applications Filed and Issued in the USPTO, the EPO and CIPO

Type of Lifeform	USPTO		EPO		CIPO	
	Issued	Pending	Issued	Laid Open[a]	Issued	Laid Open[a]
Plants	176	≅ 600	50-100	≅ 470[b]	0	≅ 140
Animals	7	≅ 370	1[c]	≅ 238[b]	0	≅ 32

Notes:

[a] Laid open patent applications do not include those applications filed within the last 18 months.

[b] About 60 percent of the 780 patent applications relating to plants (i.e., 470) have per se claims to plants; about 95 percent of those relating to animals (i.e., 238) have per se claims to animals.

[c] There is no moratorium on animal patents, since this is not provided for by the European Patent Convention and there is no delay in examination. Other cases were examined or are in the course of examination, and soon further animal patents will be issued. [248].

[248] Gugerell, C. European Patent Office, personal communication to J. Langford, Intellectual Property Policy Directorate, Industry Canada, November 9, 1994. The letter refers to an annexed part of a decision of an opposition division

Sources: Mr. Barry Richmond, Head of the Biotech Examination Unit of the USPTO (November 2, 1994);
Mr. Christian Gugerell, Director of Examination Unit Genetic Engineering and Mr. Rainer Osterwalder, Public
Relations Dept. of the EPO (November 9, 1994 and November 3, 1994 respectively); and Dr. Isaac Ho, Head of Biotechnology Examination Unit of CIPO (November 3, 1994).

In recent correspondence with the IPPD, Christian Gugerell, Director of Examination Unit Genetic Engineering, EPO, noted that the wording of the EPC poses particular difficulties regarding the patentability of plants and animals in Europe. Indeed, article 53(b) of the EPC expressly states that plant and animal varieties, as well as biological processes, are unpatentable. This exception does not apply, however, to essentially microbiological processes used to obtain such plants and animals. The European situation is further complicated by the presence of article 53(a) in the EPC which provides that inventions contrary to "ordre public" or morality are not to be patented. Article 53(a) has been put forward in the Harvard oncomouse case, on the basis that animal suffering is immoral. A patent was issued on the oncomouse in 1992, but 17 oppositions were lodged against it. It is likely that a decision in opposition will be reached in late 1995.[249]

There were 101 biotechnology patent applications received in Canada listing Canadian applicants, and 1,589 listing U.S. applicants. Table 6.8 shows the number and distribution of these applications by type of applicant.

Table 6.8
Distribution of Laid Open Canadian Biotechnology Patent Applications from Canadian and U.S. Applicants by Type: 1989-1992

Type of Applicant	Canadian Applications		U.S. Applications	
	No.	%	No.	%
Companies	31	30.7	974	61.3
Individuals	30	29.7	214	13.5
Hospitals/research centres	12	11.9	163	10.3
Universities	17	16.8	166	10.4
Government	11	10.9	71	4.5
Indian tribe	0	0.0	1	0.1
Total	**101**	**100**	**1,589**	**100**

Source: IPPD patent data base of PCT laid open applications claiming lifeforms.

- Canadian companies file about one third the number of patent applications of their U.S. counterparts (assuming a 10:1 ratio for comparison purposes between the United States and Canada). The number of applications filed by other types of

on a plant case

[249] Ibid

Canadian applicants is more in line with the expected 10:1 ratio.

The finding that U.S. companies file three times the number of patent applications as their Canadian counterparts may be due to the fact that U.S. biotechnology companies are better capitalized than Canadian companies or that U.S. firms are at a more advanced stage of development. It may also be that the previously reported finding of chronic underfinancing for Canadian firms contributes to their inferior development vis-à-vis U.S. firms.

- The National Research Council filed the most applications of any Canadian applicant during the 1989 to 1992 period. With this exception, few Canadian applicants filed more than one biotechnology patent application in any given year. In contrast, many U.S. applicants filed more than one Canadian biotechnology patent application in any given year during the 1989 to 1992 period.

These findings suggest that Canadian firms are at an early stage of development. Their patents relate to specific technology discoveries. Multiple patents by U.S. applicants suggest their biotechnology products are closer to market entry.

Table 6.9 shows the distribution of these applications by class of applicant.

- Canadian resident applicants file proportionately more patent applications in the classes relating to agriculture than their U.S. counterparts. This is likely because Canada has a thriving agricultural industry.

- Canadian resident applicants tend to file about the same proportion of patent applications for genetic engineering and medical preparations as their U.S. counterparts.

Table 6.9

Distribution of Canadian Biotechnology Patent Applications from Canadian and U.S. Applicants by Class: 1989-1992

Class Number	Class Description	Canadian Applicants (%)	U.S. Applicants (%)
C12N	Microorganisms or enzymes; compositions thereof; propagating, preserving or maintaining microorganisms; mutation or genetic engineering.	51.0	50.0
C12M	Apparatus for enzymology or microbiology.	0.0	1.0
C12P	Fermentation or enzyme-using processes to synthesize a desired chemical compound or composition or to separate optical isolmers from a racemic mixture.	13.0	17.0
C12Q	Measuring or testing processes involving enzymes or microorganisms; compositions or test papers therefor; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes.	12.0	11.0
C12S	Processes using enzymes or microorganisms to liberate, separate or purify a pre-existing compound or composition; processes using enzymes or microorganisms to treat textiles or to clean solid surfaces of materials.	0.0	0.4
A61K	Preparations for medical, dental or toilet purposes.	15.0	18.0
A01H	New plants or processes for obtaining them; plant reproduction by tissue culture techniques.	1.0	0.3
A01K	Animal husbandry; care of birds, fishes, insects; rearing or breeding animals, not otherwise provided for; new breeds of animals.	2.0	0.3
A01N	Preservation of bodies of humans or animals or plants or parts thereof; biocides as disinfectants, as pesticides, as herbicides; pest repellants or attractants; plant growth regulators.	6.0	2.3
Total number of applications		**101**	**1,589**

Source: IPPD patent data base of PCT laid open applications claiming lifeforms.

Table 6.10 shows the distribution of place of residence of the inventor for the 101 biotechnology patent applications from Canadian applicants in the IPPD data base. Not surprising, Ontario and Quebec led other provinces. Alberta and Saskatchewan had proportionately more than would be warranted by the distribution of biotechnology firms in the country while British Columbia had fewer. The residence of the inventor for 10 of the 101 patent applications (10 percent) was outside Canada.

Table 6.10
Distribution of Laid Open Biotechnology Patent Applications from Canadian Applicants by Residence of Inventor: 1989-1992

Province	No.	%
Ontario	48	47.5
Quebec	21	20.8
Alberta	9	8.9
Saskatchewan	8	7.9
British Columbia	4	4.0
Newfoundland	1	1.0
United States	4	4.0
United Kingdom	2	2.0
Austria	1	1.0
India	1	1.0
Unknown	2	2.0
Total	**101**	**100.0**

Source: IPPD patent data base of PCT laid open applications claiming lifeforms.

Between October 1, 1989 and September 24, 1993:

- Applicants filed 6,646 patent applications for biotechnology inventions in Canada (Table 6.4).

- The rate of request for examination of biotechnology patent applications was 17.42 percent (1,158 requests) compared with 30.81 percent for all non-biotechnology patent applications.

- The annual distribution of requests for examination of biotechnology patent applications was as follows:

  - in 1989, there were 19 requests;
  - 1990 had 170 requests;
  - 1991 had 223 requests (beginning in 1992, requests for examination applied to patent applications filed in any of the years 1989 to 1992);
  - 1992 had 369 requests; and
  - in 1993, there were 377 requests.

- As the data indicate, applicants of patent applications for biotechnology inventions request examination of their applications at a much lower rate than applicants of patent applications for other inventions. This is discussed later in this chapter.

- The average time between the date of filing of a biotechnology patent application and the date of request for examination was 12.57 months. Note that section 38.1 of the Patent Rules allows inventors to wait seven years before making a request for examination. The average time from the date examination of a patent application was requested to the date of issuance of the first office action on the merits of the application was 19 months.

- Of the 1,158 filed biotechnology patent applications and requested examinations, only five (0.4 percent) resulted in a patent being issued in the years 1989 to 1992. An explanation is that CIPO gives priority to patent applications filed under the old *Patent Act*.

The calculation of the average time from the date when examination of a patent application was requested to the date of issuance of the patent was not measured as it would not have been significant due to the small number of patents which have issued.

6.2.2 Analysis of IP Data from the Biotechnology Survey

This section analyzes survey results on the behaviour of Canadian biotechnology firms with regards to the use of IPRs. Table 6.11 shows the percentage of firms using particular methods to protect IP over the survey period (1989 to 1993).

Table 6.11

Percentage of Firms Using Various Methods to Protect Intellectual Property: 1989-1993

Methods of IP Protection	Size of Firm (No. of Employees)				
	1-10	11-25	26-100	101+	Total
Patents	44%	52%	84%	83%	57%
Trade secrets	49%	59%	60%	38%	52%
Trademarks	28%	50%	61%	28%	37%
Copyrights	14%	7%	17%	27%	14%
Industrial designs	7%	24%	16%	11%	11%
Licencing	5%		4%		4%
Plant breeders' rights	3%	10%	8%	5%	5%

Note: See Footnote [250].

- Canadian biotechnology firms protect their technology using patents (57 percent), trade secrets (52 percent), trademarks (37 percent), copyrights (14 percent), industrial designs (11 percent), licensing (4 percent) or plant breeders' rights (5 percent).

- Intermediate (26 to 100 employees) and large-sized firms (101+ employees) use patents more than any other type of protection..

- Very small (1 to 10 employees) and small-sized (11 to 25 employees) firms use trade secrets more than patents.

Table 6.12 shows the average number of times firms used the various methods of IP protection between 1989 and 1993.

- Large firms used patents more often than any other size of firm to protect their technology. (The large firms filed about five patent applications per year on average, compared to an average of two per year for intermediate firms and one per year for other sizes of firms.

- Intermediate-sized firms used trade secrets, trademarks, copyrights and industrial designs more than all other sizes of firms to protect their technology.

- Very small firms used plant breeders' rights more than all other sizes of firms to protect their technology.

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[250] The percentages shown are based on the number of firms in the overall sample, that is, 88 (1-10), 30 (11-25), 24 (26-100), 14 (101+), 156 (Total).

Table 6.12

Average Number of Times Firms Used Various Methods to Protect IP

Methods of IP Protection	Size of Firm (No. of Employees)				
	1-10	11-25	26-100	101+	Total
Patents	4.6	5.9	10.8	24.4	9.3
Trade secrets	6.8	6.1	16.9	11.2	9.1
Trademarks	7.0	4.6	7.6	6.0	6.7
Copyrights	13.6	3.6	16.0	5.8	11.7
Industrial designs	21.8	9.0	9.1	4.0	12.4
Plant breeders' rights	17.0	1.9	1.5	2.0	5.7

Note: See Footnote [251].

Table 6.13 shows the average reported effectiveness of various methods used by firms to protect their technology.

- Small and large-sized firms consider patents to be slightly more effective than trade secrets in protecting technology.
- Very small and intermediate-sized firms consider trade secrets to be slightly more effective than patents.
- All sizes of firms felt patents and trade secrets were moderately to quite effective as IP protection measures. Industrial design was considered quite effective, trademarks and copyrights only slightly less effective and plant breeders' rights moderately effective.

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[251] The number of firms which responded for each method of IP protection is shown (with size of firm in brackets):
Patents: 39 (1-10), 16 (11-25), 20 (26-100), 11 (101+), 86 (Total).
Trade Secrets: 43 (1-10), 18 (11-25), 15 (26-100), 6 (101+), 82 (Total).
Trade Marks: 23 (1-10), 15 (11-25), 14 (26-100), 4 (101+), 56 (Total).
Copyrights: 12 (1-10), 2 (11-25), 4 (26-100), 4 (101+), 22 (Total).
Industrial Designs: 6 (1-10), 7 (11-25), 4 (26-100), 1 (101+), 18 (Total).
Plant Breeders' Rights: 3 (1-10), 3 (11-25), 2 (26-100), 1 (101+), 9 (Total).

Table 6.13[a]

Average Reported Effectiveness of Various Methods Used by Firms to Protect IP[b]

Methods of IP Protection	Size of Firm (No. of Employees)				
	1-10	11-25	26-100	101+	Total
Patents	3.60	3.87	3.41	3.58	3.59
Trade secrets	3.80	3.73	3.82	3.35	3.76
Trademarks	3.84	3.12	3.85	2.78	3.61
Copyrights	3.78	2.00	4.01	3.47	3.68
Industrial designs	4.00	4.04	4.51	3.00	3.97
Plant breeders' rights	3.00	3.06	3.00	4.00	3.18

Notes:

[a] See Footnote [252].

[b] Respondents chose the effectiveness level of each IP method from the following list: Extremely effective (5); Quite effective (4); Moderately effective (3); Quite ineffective (2); Extremely ineffective (1).

According to our survey:

- The likelihood of a Canadian biotechnology firm entering into an agreement either to grant IP rights to, or acquire IP rights from, another firm (Canadian or foreign) increased with the size of firm (Table 6.14):
  - 41 percent of the very small firms;
  - 42 percent of small firms;
  - 63 percent of intermediate firms; and
  - 73 percent of the large firms.

Table 6.14

Percentage of Firms which Entered into Agreements Granting Rights to (or acquiring rights from) Another Firm to Use IP

Size of Firm (No. of Employees)				
1-10	**11-25**	**26-100**	**101+**	**Total**
41%	42%	63%	73%	48%

Note: See Foot note [253].

[252] Ibid

[253] The percentages shown are based on the number of firms in the overall sample, that is, 88 (1-10), 30 (11-25), 24 (26-100), 14 (101+), 156 (Total).

- The likelihood of a firm entering into an agreement with another firm varied according to sector (Table 6.15). Across all sectors, the average is 48 percent as shown in Table 6.14:

  - research firms, 63 percent;
  - health care firms, 58 percent;
  - supplier firms, 49 percent;
  - agriculture firms, 43 percent;
  - resource firms, 41 percent; and
  - environmental firms, 28 percent.

These IP indicators point to accelerating commercialization activity in the larger firms and in those sectors with the earliest start-ups in biotechnology product development.

Table 6.15

Percentage of Firms which Entered into Agreements Granting Rights to (or acquiring rights from) Another Firm to Use IP

Sector						
Health	**Agri.**	**Env't.**	**Supp.**	**Res'ch.**	**Res'ce**	**Total**
58%	43%	28%	49%	63%	41%	48%

Notes:
See Footnote [254]
Abbreviations: Agri= Agri-food, Env't= Environment, Supp = Suppliers, Res'ch = Research, Res'ce = Resources.

- Large and very small-sized firms granted patent rights to other Canadian firms more than small and intermediate firms did (Table 6.16).

- Intermediate and very small-sized firms granted rights to trade secrets to other Canadian firms more than large and small firms did.

The pattern is slightly different when respondent firms granting rights to foreign firms are considered. Foreign firms were considered off-shore firms. Multinationals with divisional offices in Canada were considered Canadian.

- A larger share of intermediate and large-sized firms were involved in granting patent rights to foreign firms than were very small and small firms.

- Intermediate and large-sized firms granted more trade secrets to foreign firms than did very small and small firms.

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[254] The percentages shown are based on the number of firms in the overall sample, i.e., 32 (Health), 15 (Agri-food), 21 (Environment), 48 (Supplier), 21 (Research) and 19 (Resources).

- When all agreements, whether to foreign or Canadian firms, are combined, the large and intermediate-sized firms granted more patent rights and trade secrets than did the very small and small firms (Table 6.16).

Table 6.16

Firms Granting Rights as a Percentage of All Biotechnology Firms which Entered into IP Agreements

Methods of IP Protection	Size of Firm (No. of Employees)				
	1-10	11-25	26-100	101+	Total
Percentage of Firms which Granted Rights to Canadian Firms					
Patents	24%	21%	7%	30%	20%
Trade secrets	28%	7%	30%	22%	25%
Trademarks	6%		6%		4%
Copyrights	8%				4%
Industrial designs	8%		6%		5%
Plant breeders' rights		7%			1%
Percentage of Firms which Granted Rights to Foreign Firms					
Patents	16%	7%	32%	29%	21%
Trade secrets	22%	8%	36%	39%	26%
Trademarks	5%		33%	8%	12%
Copyrights	11%	7%	7%		8%
Industrial designs			13%		3%
Plant breeders' rights		7%			1%
Percentage of Firms which Granted Rights to Canadian and/or Foreign Firms					
Patents	29%	28%	38%	45%	34%
Trade secrets	39%	15%	55%	46%	41%
Trademarks	11%		39%	8%	16%
Copyrights	11%	7%	7%		8%
Industrial designs	8%		19%		9%
Plant breeders' rights		7%			1%

Note: See Footnote [255].

Some interesting patterns emerge (Table 6.16).

- Trade secrets are preferred over patents when firms grant IP rights to other firms.

Possible explanations are that the cost of patent protection is so prohibitive that a larger proportion of Canadian biotechnology firms choose the more direct and inexpensive route of trade secrets, or that trade secrets are the preferred route for protecting process or manufacturing technologies. Or perhaps, trade secrets are the preferred means of protecting IP because it is easier to protect the secret within small firms than within larger firms. Also, the fact that the percentages of patent or trade secret agreements with any other firm,

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[255] The sample sizes are based on the number of firms (by size of firm) which entered into agreements over the last five years granting rights to, or acquiring rights from, another firm to use intellectual property: 36 (1-10), 13 (11-25), 16 (26-100), 10 (101+), 75 (Total).

foreign or domestic, are greater than with Canadian or foreign firms alone suggests little overlap.

- Individual firms will choose either to deal with another Canadian firm or with a foreign firm but not necessarily with both at the same time (at least within the survey period). Since 34 percent of all firms granted patent rights to some other firm, while 20 percent granted these rights to Canadian firms, and 21 percent granted them to foreign firms (totalling 41 percent), then only 7 percent of all Canadian biotechnology firm respondents granted patent rights to both Canadian and foreign firms.

This pattern appears across nearly all firm sizes and types of IP agreements. Plant breeders' rights are one of the few exceptions.

- This suggests that most firms make clear choices either to export their technologies or to keep them in Canada.

- Canadian firms acquired more patent rights to technology than they granted, 47 percent versus 34 percent. This pattern was most pronounced for large and small-sized firms, and less so for very small and intermediate firms.

This suggests that biotechnology development in Canada has resulted in more in-licensing than out-licensing activity (tables 6.16 and 6.17).

- The exchange of trade secrets seemed to be evenly balanced since 42 percent acquired trade secrets from some other firm, and 41 percent granted trade secret rights to some other firm.

- Large-sized firms tended to grant trade secret rights more than acquire them while very small firms did the opposite. In general, large firms would be expected to have more trade secrets to barter than would any other size of firm.

- All firms (and large firms in particular) acquired patent rights from a foreign firm more often than from another Canadian firm, the only exception to this observation being small firms.

Table 6.17

Firms which Acquired Rights as a Percentage of All Biotechnology Firms which Entered into IP Agreements

Methods of IP Protection	Size of Firm (No. of Employees)				
	1-10	11-25	26-100	101+	Total
Percentage of Firms which Acquired Rights from Canadian Firm					
Patents	10%	48%	12%	23%	17%
Trade secrets	25%	34%	24%	24%	26%
Trademarks	8%	8%			5%
Copyrights		7%		16%	3%
Industrial designs	3%				1%
Percentage of Firms which Acquired Rights from Foreign Firm					
Patents	34%	24%	38%	69%	39%
Trade secrets	22%	24%	42%	24%	28%
Trade marks	5%	17%	19%	16%	12%
Copyrights			6%	16%	4%
Industrial designs	3%		6%		3%
Percentage of Firms which Acquired Rights from Canadian and/or Foreign Firms					
Patents	39%	56%	44%	69%	47%
Trade secrets	41%	41%	55%	24%	42%
Trade marks	10%	17%	19%	16%	14%
Copyrights		7%	6%	16%	5%
Industrial designs	5%		6%		4%

Note: See Footnote [256].

- In contrast, acquisition of trade secrets from domestic and foreign firms was relatively balanced among all firms (28 percent versus 26 percent) as well as among all firms regardless of size.

- A greater proportion of trade secrets was acquired from domestic firms by small-sized Canadian biotechnology firms (34 percent versus 24 percent) while a greater proportion was acquired from foreign firms by intermediate biotechnology firms (42 percent versus 24 percent).

6.3 Current IP Issues

Interviews with various members of the Canadian biotechnology community form the basis for the material in this section. The discussions included domestic and international patent issues and strategies, the use of trade secrets, IP ownership of R&D investments and how these relate to the development of a Canadian biotechnology industry. Reference to some of the related IP literature is also included.

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[256] Ibid

Because health care dominates commercialization initiatives and sales activity in biotechnology, most Canadian IP practitioners serve the health care sector. Consequently, the IP issues concerning these professionals focus on this sector, in general, and pharmaceutical products, in particular.

The views of Canadian health care biotechnology companies depend on whether the company is a small, new biotechnology firm (NBF), large multinational or Canadian generic drug company. Canadian NBFs tend to divide between those seeking concessions from the government to nurture development of the industry and those seeking a level playing field or harmonization with perceived global norms (the multinational perspective). When it comes to biotechnologically derived drugs, however, there is some congruence between the views of Canadian NBFs and generic drug companies.

IP practitioners usually represent either large multinationals or Canadian generic drug companies, but never both. In some instances, they will represent NBFs and *either* large multinationals *or* generic drug companies. However, established corporations (i.e., the large multinationals) overwhelmingly dominate the business (and hence the views) of the IP practitioner community which is based primarily in central Canada. For this reason, the views of Canadian IP practitioners are dominated by domestic commercialization issues faced by the multinationals rather than by international IP issues associated with pursuing global IP strategies. The IP practitioner interviews below reflect this reality. To the extent possible, we have attempted to redress this imbalance with supplementary research woven into the text.

6.3.1 Canadian IP Issues

Economic Issues

R&D Investment and IP Ownership: In its latest annual report, the PMPRB noted the following data compiled by Statistics Canada for 1993 (except where noted) on the Canadian pharmaceutical sector.[257]

- The sector had:
  - 122 establishments (1991);
  - 19,900 employees;
  - investments of $322 million;
  - shipments of $4,336 million;
  - value added of $3,004 million (1991);
  - R&D expenditures of $356 million;
  - exports of $489.2 million;
  - imports of $1,602.1 million; and

[257] Patented Medicine Prices Review Board. *Sixth Annual Report* (for the period ended December 31, 1993) Ottawa, Canada, June 1994.

- a balance of trade of $1,112.9 million.

- The value of shipments of pharmaceuticals as a proportion of total manufacturing grew from 0.766 percent (1969), to 0.894 percent (1983), to 1.4 percent (1993).

- Employment, another index of performance for the pharmaceutical industry which the Eastman Commission found relevant in 1985,[258] grew from 0.74 percent of total manufacturing (1967), to 0.91 percent (1982) to 1.3 percent (1993). Some of the employment in 1982 (about 1,300 of 15,707 employees) and in 1993 was with generic firms.

The PMPRB also provided data for 70 reporting companies in 1993 with active Canadian patents pertaining to a medicine sold in Canada which are required under the *Patent Act* to report on R&D expenditures. Generally, these companies were Canadian subsidiaries of foreign multinational pharmaceutical and biotechnology firms. For these companies, total sales revenues were $4,747.6 million, and total R&D expenditures were $503.5 million (or 10.6 percent of sales revenues). The PMPRB notes that total R&D expenditures, as reported by Statistics Canada and itself, differ for methodological reasons.

Our survey showed that in 1993:

- Canadian health care biotechnology firms had total sales of $1,310.7 million (including rDNA product sales of $408.3 million) and total R&D expenditures of $337.9 million (including rDNA R&D expenditures of $256.4 million).

- The rDNA R&D expenditures were 62.7 percent of rDNA sales, while naturally occurring microorganisms (NOM) R&D expenditures were 9 percent of NOM sales.

- Total exports were $300.1 million (including rDNA exports of $63.3 million).

- The balance of trade was -$827.4 million (including an rDNA balance of trade of -$294.5 million.

The PMPRB breaks down total R&D expenditures for the 70 reporting companies in 1993 by type of R&D performer. Total R&D expenditures include equipment expenditures and allowable depreciation expenses.

- Of the remaining $477.8 million, only $119.5 million was spent in universities and hospitals (25 percent), the rest being spent by the patentees (59 percent), other companies (8.3 percent) and others (7.7 percent).

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[258] *Report of the Commission of Inquiry on the Pharmaceutical Industry.* Minister of Supply and Services Canada, Ottawa, Canada, 1985. Cat. No. CP32-46/1985E. ISBN 0-660-11835-1.

- Of the total R&D expenditures, $120.7 million was spent on basic research (25.3 percent), the remainder being spent on clinical and preclinical research trials, drug regulation submissions, bio-availability studies and phase IV clinical trials.[259]

We asked a fundamental question: how much of the total R&D expenditures of $503.5 million was spent on discovery research leading to IP owned by Canadians? The country of residence of the owner is pertinent to the location of subsequent investments to develop and manufacture the underlying technology. The only component of these R&D expenditures which may give rise to Canadian IP ownership rights is the university/hospital component. Through our interviews, we discovered that many such companies retain explicit IP ownership or *de facto* ownership in the form of the right of first refusal to acquire ownership of any biotechnological discoveries made during the course of university/hospital-based R&D in this country funded by these companies. We concluded that significantly less than the total R&D spending of $503.5 million (by the 70 reporting companies in this country) was spent on research with long-term, value-added economic significance for Canada. Assessing the impacts of R&D spending would require significantly more research.

The Association of University Technology Managers (AUTM) has prepared its own *Technology Transfer Practice Manual*, an international reference guide for technology transfer offices at universities, teaching hospitals and other organizations. The Manual addresses issues of IP ownership in industry-sponsored research at such institutions and provides samples of sponsored research agreements (viz., the Harvard University sample).[260] A number of Canadian research institutions use similar agreements. Others do not. In at least one major Canadian university, there is a complete spectrum of arrangements regarding the ownership of the IP deriving from industry-sponsored research. The Harvard research agreement begins with a defining statement on IP: "All rights in inventions, discoveries, biological materials or software created in the course of the Research shall be the property of HARVARD and their disposition shall be at HARVARD's sole discretion."

At the Canadian university mentioned above, there is a university technology transfer (TT) office which handles a very small number of agreements, and there are at least three Industry Research Assistance Program (IRAP) sponsored TT officials in other parts of the university conducting separate business. In addition, individual students and professors enter directly into agreements with industry without participation by the university.

The National Science and Engineering Research Council (NSERC) sponsors joint cost-shared university–industry programs. Most programs are geared toward pharmaceutical R&D, and the industry sponsor is expected to provide at least 50 percent of the direct

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[259] Patented Medicine Prices Review Board. *Sixth Annual Report* (for the period ended December 31, 1993) Ottawa, Canada, June 1994.

[260] Association of University Technology Managers, Inc. (AUTM). *The AUTM Technology Transfer Practice Manual.* 1993. Contact: AUTM, 71 East Avenue, Suite S, Norwalk, CT 06851-4903.

funding requirements.[261] A concerned academic from the above-mentioned university noted that NSERC had reduced the number of fellowships to between 300 and 400 for the 1993-94 year. NSERC now provides "industrial scholarships" worth about $17,000 with $5,000 to be provided by industry and the remainder by NSERC. These are master's and doctoral level scholarships and require the student to work two months a year for the company. The original research in the student's thesis cannot be released or published for two years. Furthermore, in agreeing to work within the company, the student will undoubtedly be bound by confidentiality agreements which will further encumber his or her ability to publish and take ownership of the research.

The IP concerns at this institution boil down to certain fundamental issues. Who owns the research (the student, professor, university, general public or industry)? How free are staff and students to do independent research? Concerned staff at the university are now drafting ethical guidelines in an attempt to bring some order to university–industry research agreements.

The university's problems also reflect larger issues of IP ownership affecting R&D investments across the country. How much value does Canada derive from industry-sponsored biotechnology research, particularly when control of the research value resides off-shore? Is there a strategic role here for the government to play? Are there ways government can encourage the development of strategic alliances with Canadian NBFs which will infuse the industry with much needed investment capital to stimulate Canadian R&D and manufacturing activity? We believe there are opportunities.

Recently, a major established corporation (Hoffman-LaRoche) filed a lawsuit in a U.S. District Court against Promega Corp., a bioscience company, to obtain a ruling on the "infringement" of its patents on a method for amplifying DNA [a method known as polymerase chain reaction (PCR) and described in Chapter 3]. The court case places in doubt the practice by universities and research laboratories of buying patented products and procedures, such as for computers and biotechnology, for the purpose of scientific research. The issue could potentially double the cost of research by forcing the payment of licensing fees to patent holders for the use of their patents in experiments. Ironically, the PCR technology originated in American university laboratories. Unsettled by the potential for diminished academic research that typically helps them make new products, U.S. pharmaceutical companies, including Merck & Co., have offered their support to Promega. Promega is soliciting help from the White House and Congress, arguing that Hoffman-LaRoche's move threatens U.S. competitiveness.[262]

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[261] National Advisory Council on Pharmaceutical Research. *A strategy for the development of a growing sector: pharmaceutical research.* Health and Welfare Canada, 1991.

[262] Carlton, J. "Right to use patented products in university research threatened." *Wall Street Journal*, May 25, 1995, p. B12

Global Patent Strategies: There are at least two perspectives on global patent strategies, that of firms and of governments. These perspectives are in constant flux as firms adapt their strategies to domestic and international legislative and regulatory developments.

It has been widely noted that the United States is the only country in the world to follow the first to invent rule for patenting. All other countries follow the first to file rule. The opinion was expressed that this gives the United States a monopoly under NAFTA/GATT agreements. However, the U.S. first to invent rule is invoked only in disputes between two applicants concerning the same invention. Proof of the first inventor requires examination in detail of the disputants' laboratory and other data and usually involves prolonged and costly litigation. The process is referred to as "conflict resolution" by CIPO and as "interference resolution" by the USPTO. For applications for the same invention filed with CIPO before October 1, 1989, there is provision under the *Patent Act* for conflict resolution to determine the first inventor and, hence, the valid patent application. Following October 1, 1989, the date of filing of the patent application is considered to determine the first inventor in all countries except the United States. A CIPO representative noted that most of the backlog in the examination of filed patent applications in their office relates to the conflict resolution issue for applications filed before October 1, 1989.

It is important to note that before October 1, 1989, patent applicants in Canada enjoyed a two-year grace period following the disclosure of their invention in a scientific conference, publication or otherwise before being required to file a patent application for the same invention. A second applicant for the same invention who filed before the first applicant's filing date but after the disclosure date would have his or her application rendered invalid (unless he or she could prove, in a conflict resolution process, that the date of invention preceded that of the first applicant). Before October 1, 1989, any applicant for a Canadian patent could enjoy this grace period. After this date, only applicants who were also the inventors enjoyed the grace period. For all other applicants, such prior disclosure would render their patent applications invalid. The grace period for post-1989 Canadian patent applications has been reduced to one year. The Canadian grace period into line with that of the United States.

The remaining difference for U.S. patent applicants is that they do not have to be the inventors. Anybody, including a corporation, can file for a U.S. patent and still enjoy the one-year grace period.

In Section 4.4.1, we noted the inherent conflict between a scientist's responsibility to publish research (to advance knowledge and gain academic merit or additional funding) and the industry's insistence on confidentiality until domestic and international patent applications have been filed. Given the existence of the one-year grace period in both the U.S. and Canadian patent regimes, it is possible for a Canadian academic inventor to disclose his or her discovery first through publication or otherwise, then file a patent application in Canada within the grace period, and still preserve ownership of the patent application for the invention. Apparently, this grace period does not exist in other patent regimes (viz., European countries or Japan). In certain European countries, the inventor may apply to the patent office in his or her country for permission only to *exhibit* the

discovery, and not otherwise disclose it before filing a patent application. The rule is probably a concession to industry to allow a limited form of disclosure (viz., exhibition) at a trade fair for promotional or other business purposes.

In all countries including Canada and the United States, the date of filing of the patent application determines the priority date for the patent's claims in all countries subscribing to the Paris Convention. Under the Convention, the applicant in the priority country has one year to file patent applications in all other countries in order to preserve his or her patent status for those claims. Until June 8, 1995, the U.S. patent term extended for 17 years following the date of issuance of the given patent. After this date the term for all issued U.S. patents extends for 20 years from the date of filing of the patent application. There is scope, however, within U.S. patent law for patent term restoration beyond the 20 years on appeal for reasons related to excessive regulatory approval delays.

One practitioner gave an example of how the disparities between Canada and the United States have caused at least one Canadian NBF to relocate its business in the United States (although the officers of the company live in Canada) so the firm would benefit from a U.S. address. The firm was dissatisfied with delays in obtaining patent protection in Canada and with Canadian regulatory hurdles. Furthermore, the firm expected that a U.S. residential address would enhance its ability to form strategic alliances, raise capital, and obtain regulatory clearances and patents in the United States. A number of persons remarked during interviews that the U.S. Food and Drug Administration (FDA) and the USPTO favour American firms.

Interviewees emphasized that it is critical for the federal government to monitor the status and effect of proposed and enacted legislation in other countries on Canadian NBFs. Examples given included the U.S. Boucher Bill, U.S. patent practices, i.e., reduction to practice, and the U.S. orphan drug legislation (see Section 6.3.2). When proposed or enacted legislation harms Canadian NBFs, interviewees suspected that the federal government should work with other countries to try to reduce the adverse impact of their legislation.

Major advances in the life sciences over the last 15 years have led to an increased number of biological drugs produced using biotechnology techniques. Biotechnology, particularly recombinant methods, allow manufacturers to produce sufficient quantities of these medicinal preparations for therapeutic use. Although the U.S. Supreme Court has held that living organisms are patentable, naturally occurring compounds and compositions themselves are not patentable in the United States because they are not considered novel. Products that exist in nature may be considered patentable if they are given a form, quality or function they do not possess in the natural state or otherwise meet all other criteria for patentability. Those who produce old drugs with the new techniques of biotechnology tend to seek patent protection for the methods by which they produce the drug; the bases for these patents are referred to as "process claims."

In 1984, Congress passed the *Drug Price Competition and Patent Term Restoration Act* (Public Law 98-417), which allowed the USPTO to add up to five years to the patent term of drugs when the patent term was eroded by regulatory review. As of May 1992, the

USPTO had issued 142 patent extensions most often for a period of two years beyond the statutory 17-year exclusivity. In addition, from time to time, the U.S. Congress has passed special legislation granting additional patent extensions for individual drugs.[263]

Once patents protecting the exclusive marketing rights of a drug expire, the manufacturer of the original form of the drug often seeks to maintain its market share by developing new, but related products. These new products may include previously unmarketed dose forms of the drug, e.g., one requiring less-frequent or easier administration. Once on the market, physicians and patients may prefer this dose form over generic versions of the old dose form. Alternatively, the originator firm may develop a new (and patentable) drug product that is chemically related to the first but offers some clinical superiority. For example, the new drug may have fewer adverse reactions than the first generation product that is losing its patent protection. Although all companies theoretically may attempt to develop follow-on products to drugs losing patent protection, U.S. federal law may offer the originator company an advantage in developing them more quickly. In a series of legal decisions, U.S. federal courts have determined that researchers may use patented materials and processes for non-commercial scientific inquiry, but any research related to a possible commercial product constitutes a patent infringement. Hence, the originator may conduct R&D activities on follow-on products, while all other competitors must wait until any relevant patents expire before beginning to develop their own.

Furthermore, the *Drug Price Competition and Patent Term Restoration Act* contains a provision that may reinforce the advantage originator firms have in getting follow-on products to market. U.S. law provides for three years of market exclusivity for companies receiving approval of a new drug application (NDA) that is not for a new chemical entity or of a supplemental NDA for a new use of an already approved drug. To be eligible, the new or supplemental NDA must be based on new clinical research (other than bioavailability studies) conducted or paid for by the drug's sponsor. This is essential for FDA approval.[264]

Published articles reviewed for this study indicated that IP strategies of multinational biotechnology firms include:

- obtaining the broadest possible claims to their biotechnology invention in patents in important markets; and
- aggressively defending their patents and suing others for patent infringement.[265]

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[263] U.S. Office of Technology Assessment. *Pharmaceutical R&D: Costs, risks and rewards.* USOTA, Report No. OTA-H-522,Washington, DC, February 1993, pp. 225 ff.

[264] Ibid

[265] Zahralddin, R. "Note: The Effect of Broads Patent Scope on the Competitiveness of United States Industry." *Delaware Journal of Corporate Law*, Vol. 17, 1992, p. 949.

Patents may also carry infringement value that translates into revenue through litigation instead of through market share. Another reason for seeking patents is to have a patent portfolio with which to negotiate licence agreements.[266] Without a large and steady stream of capital, Canadian NBFs find it difficult to adopt a strategy which includes seeking and enforcing patents in markets outside of Canada.

Interviews with practitioners and members of the Canadian biotechnology industry indicated that their current domestic IP strategies include:

- deferring examination of Canadian biotechnology patent applications because of delays in patent prosecution and uncertainty in the scope of protection;
- seeking broad blocking patents and broad blocking patent applications; and
- dedicating patents covering patented medicines to the public in order to circumvent the jurisdiction of the PMPRB.

Under the strategy of deferring examination, a company will file a patent application but defer examination. In doing so, it derives at least three benefits from:

- the date of first filing of its application;
- the increased uncertainty (and costs) to possible competitors from the presence of the Canadian application; and
- the risk of potential sales losses resulting from any possible patent refusal.

IP practitioners and members of the Canadian biotechnology industry revealed that many Canadian NBFs and multinational biotechnology firms have chosen not to commercialize products in Canada because of the small market size. In their view, too much capital (in relation to possible revenue) is required to obtain effective IP protection, litigate the validity of broad blocking patents and obtain regulatory clearance of biotechnology products. At least some of these biotechnology products probably would fall under the U.S. orphan drug legislation outlined below. Similar drug treatment market niches in Canada would be too small to warrant the noted investments.

A generic drug industry IP practitioner raised an issue concerning the delay in the filing of patents from one country to the next. If a company files first in the United States and second in Canada one year later, then the U.S. patent would expire one year sooner. But a Canadian-based generic drug company would not be able to manufacture in Canada for export to the U.S. market for that one year during which the patent was still in effect in this country. Hence, Canadian generic drug exporters are disadvantaged by this rule which enables the U.S. patent holder to corner the generic market for its product in the United States while the Canadian company is effectively blocked from market entry. His recommendation was that patent terms should be keyed to the date of filing of the first application (usually in the company's home country). In his view, this would remove the

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[266] Wyatt S., G. Bertin and K. Pavitt. "Patents and Multinational Corporations: Results from Questionnaires." *World Patent Information*, Vol. 7, 1985, p. 196.

disadvantage.

However, the practitioner's recommendation that patent terms be keyed to the date of filing of the first application would be contrary to article 4*bis* ("Independence of Patents Obtained for the Same Invention in Different Countries") of the Paris Convention for the Protection of Industrial Property (as described in Section 6.1.4).

Harmonization: We asked members of the Canadian biotechnology community whether Canada's policies, laws and regulations on IP protection for biotechnology inventions lag behind those of Canada's major trading partners. Their comments confirmed the research findings sketched out in Section 6.1 (and Table 6.1) that the United States leads the rest of the world in providing IP rights in the field of biotechnology. Europe follows, and Canada lags behind both in its adoption of IP policies, laws and regulations, and in its issuance of patents on plants and animals (Table 6.7). While many members of the biotechnology community supported harmonization with other countries, consumer organizations opposed this move, voicing concern for the impact of harmonization on the availability and pricing of biotechnology products.

Nurturing Canadian Biotechnology: Members of the Canadian biotechnology industry were divided over the issue of concessions for Canadian NBFs compared to non-resident biotechnology firms (i.e., multinationals). Of course, advocates of the no concession point of view were practitioners for, or representatives of, multinational firms. Others, however, expressed their support for IP policies, laws and regulations which would favour Canadian NBFs. They pointed to the benefits U.S. firms receive from U.S. policies, laws and regulations, and indicated that Canadian firms should similarly benefit from Canada's policies, laws and regulations.

Canada's biotechnology industry was divided over the issue of preferential treatment. Certain Canadian biotechnology firms (not controlled by multinationals) supported the view of preferential treatment. Other Canadian biotechnology firms (also not controlled by multinationals) have advocated a level playing field. However, a recent request by the Ontario Biotechnology Council for development funds from the province to build a biotechnology manufacturing capability suggests an inconsistency in this point of view. Of course, multinationals advocated the level playing field philosophy. With the increased internationalization of commercial enterprise, the trend is toward increasing harmonization of policies and laws.[267] The United States, Europe and Japan have attempted, with mixed success, to co-ordinate their efforts on certain policies affecting biotechnology inventions.[268]

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[267] Langford, J. and D. Blaker. "The role of intellectual property in the competitiveness of the pharmaceutical sector." *1991 Pharmaceutical Review.* Intellectual Property Review Branch, Consumer and Corporate Affairs Canada, October 1991; Kaminski, K.T. "Disclosure of Information in a Computer-Readable Form for Biotechnology Inventions." *Canadian Intellectual Property Review.* Vol. 10, September 1993, p. 93.

[268] Kaminski, K.T. "Disclosure of Information in a Computer-Readable Form for Biotechnology Inventions." *Canadian Intellectual Property Review.* Vol. 10, September 1993, p. 93.

A number of Canadian NBFs recommended that the federal government adopt policies, laws and regulations favouring firms with a site of manufacture in Canada. Such firms urged the federal government to determine whether:

- it can provide concessions to Canadian firms which manufacture biotechnology products in Canada without contravening NAFTA and GATT; and

- Canadian firms can have the option of seeking a compulsory licence to manufacture biotechnology products in Canada where patent owners fail to manufacture such products in Canada.

Several interviewees representing innovative and generic biotechnology firms remarked that the United States is protectionist toward biotechnology firms residing in the United States, despite NAFTA. They recommended that Canada adopt protectionist measures towards Canadian biotechnology firms. They also commented that a level playing field would only help the multinationals and would not help the Canadian biotechnology industry. One interviewee commented that a number of globally competitive firms initially developed within a protectionist environment in their home countries. Examples of protectionist strategies leading to globally competitive firms included global pharmaceutical companies as well as the Japanese computer industry.

However, other interviewed representatives of Canadian biotechnology firms were adamant that concessions to Canadian biotechnology firms would harm, not help, the Canadian biotechnology industry. They warned that other countries could retaliate with protectionist countermeasures which would impede Canadian biotechnology firms from entering those markets.

A number of persons suggested that Canada should adopt more favourable laws on the payment of fees by "small entities." U.S. law enables universities, research institutes and mid-size companies to benefit from reduced fees charged by government agencies such as CIPO.

Legal Issues

Subject Matter and Scope of Biotechnology Inventions:

Patentability of higher lifeforms. While the definition of "invention" in Canada's patent legislation parallels definitions in the patent legislation of other industrialized countries,[269] CIPO does not grant patents for certain biotechnology inventions that other patent offices consider patentable.

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[269] Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." C.I.P.R, Vol.10, 1993, p. 347.

In 1985, the USPTO recognized the patentability of plants (*Ex parte Hibberd et al.*), and in 1987 the patentability of oysters (*Ex parte Allen*). In 1987, the United States Commissioner of Patents announced that non-naturally occurring non-human multicellular living organisms, including animals, were patentable. In 1988, the USPTO granted a patent on the Harvard mouse and more recently has granted patents on other transgenic mammals (Table 6.17). Despite the more activist role assumed by the USPTO in biotechnology, Zahralddin maintains that lack of guidance on an "innovation" policy has hindered the competitiveness of U.S. NBFs.[270]

The European Patent Office recognized the patentability of plants and seeds in 1989 (*Re Lubrizol Genetics Inc.*) and the patentability of the Harvard mouse in 1992. Recently, the EU's Internal Market Council, comprising trade ministers of each member state, announced that it had reached a common position on measures concerning patent protection of biotechnology inventions. It may take many years for this directive to be adopted in all EU countries. This opinion is reinforced by the European Parliament's recent rejection (on February 28, 1995) of the draft directive on the patentability of various biotechnology inventions including higher life forms.[271]

CIPO has yet to issue a patent on a plant or animal. Our interviews indicated that this policy has discouraged inventors from filing patent applications directed to this subject matter. Furthermore, these policies affect the investment climate for Canadian and multinational biotechnology firms in this country.[272]

Before the *Pioneer Hi-Bred* case, CIPO had refused to issue patents on plants without providing any justification. It relied on the decisions of the Supreme Court of Canada and the Federal Court of Appeal in *Pioneer Hi-Bred Limited v. Commissioner of Patents* in continuing to refuse to grant patents on plants. However, a number of senior Canadian IP practitioners consider certain plants to be patentable despite the *Pioneer Hi-Bred* decision.[273] The view of these practitioners is that the *Pioneer Hi-Bred* decision applies only to a new variety of soybean developed through traditional cross-breeding. Thus, they conclude that other types of plants, for example those developed through genetic engineering, are patentable provided that such plants meet the other requirements of patentability. These practitioners are also of the view that Canada's laws or regulations need not be changed in order for plants to be patentable. They reason that the definition of "invention" in Canada's *Patent Act* is sufficiently broad to support the patentability of

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[270] Zahralddin, R. "Note: The Effect of Broads Patent Scope on the Competitiveness of United States Industry." *Delaware Journal of Corporate Law*, Vol. 17, 1992, p. 949.

[271] Betts, M.T. "Memorandum on EU Biotech Patenting - EurParl Rejects." Mission of Canada to the European Union, Brussels, Belgium, March 2, 1995.

[272] Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." C.I.P.R, Vol.10, 1993, p. 347

[273] Rae, P.A. "Patentability of Living Subject Matter." *Canadian Intellectual Property Review*. Vol. 10, September 1993, p. 41.

plants and that CIPO need only change its policy to recognize that genetically engineered plants are patentable. Furthermore, they argue, there is no court decision which prevents CIPO from regarding animals as patentable. They argue that Industry Canada should formulate a well-reasoned policy on the patenting of higher lifeforms, including plants, animals and humans. One could add that this issue has economic and strategic importance for the Canadian biotechnology community.

Plant breeders' rights. Members of agricultural biotechnology firms indicated that some firms were reluctant to seek plant breeders' rights certificates under Canada's *Plant Breeders' Rights Act* because competitors could obtain compulsory and automatic licences under the existing legislation. They expressed dissatisfaction with this legislation and with the government's refusal to grant patents for plants. They noted, as well, that the absence of patent protection for plants affects their ability to raise capital and their firms' decisions to commercialize biotechnology products in Canada.

Broad blocking patents. As a relatively new science, biotechnology includes "pioneer" products and processes. Patent offices tend to issue broad patents to "pioneer" products and processes[274] because patent offices:

- are inclined to recognize the contribution of pioneer inventions;
- have insufficient resources to examine patent applications properly; and
- are experiencing political pressure to decrease the backlog of patent applications.[275]

Now that biotechnology is an established science, a number of practitioners propose that exceedingly broad claims should not be granted.[276]

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[274] Armitage, R.A. "The emerging U.S. Patent Law for the Protection of Biotechnology Research Results." *European Intellectual Property Review.* Vol. 11, 1989, No. 45-57, p. 49; Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Love, C.G. "A Survey of Recent Biotechnology and Patents Litigation in the U.S." *US Biotech*, Vol. 9, 1991, p.10.

[275] Love, C.G. "A Survey of Recent Biotechnology and Patents Litigation in the U.S." *US Biotech*, Vol. 9, 1991, p.10

[276] Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Love, C.G. "A Survey of Recent Biotechnology and Patents Litigation in the U.S." *US Biotech*, Vol. 9, 1991, p.10.; Knuth, S. And T. Pehu and H.G. Gullenberg. "Characterization of Genetic Engineering Inventions in Patent Claims." *World Patent Information*, Vol. 9, 1984, p. 229; Greenfield, M.S. "Notes - Recombinant DNA Technology: A Science Struggling with the Patent Law." *Stanford Law Review.* Vol. 44, 1992, p. 1051; Kingwell, B.G. "Functional Language and Fingerprints." *Canadian Intellectual Property Review.* Vol. 10, 1993, p. 87

Overly broad patents granted early in the history of the biotechnology industry deter entry by smaller biotechnology companies.[277] Broad biotechnology patents have claims which would include many biotechnology products and processes within their scope. New products and processes often infringe broad blocking patents, whether through literal infringement or through the doctrine of substantial equivalence.[278] Substantial equivalence means that a product or process does not have all the literal elements of the claims of a patent but takes the pith and marrow of the invention or the substance of the invention.

In a number of instances, persons stated that CIPO had granted patents that were broader in scope than patents granted by other national patent offices or granted patents for biotechnology inventions that other patent offices had refused to grant. When asked for specific examples, firms provided them, but asked that we not identify them or the products in the report.

Patents issued within one country extend rights only within that country. Therefore, broad blocking patents issued in one country, but not in a second, will prevent commercialization of corresponding products in the first, but not the second country. A broad blocking Canadian patent has an adverse impact on Canadian NBFs because it enables the owner of the patent (usually a multinational) to block Canadians from manufacturing, using or selling the claimed products or processes in Canada. A broad blocking U.S. patent has an adverse impact on Canadian NBFs seeking to enter the U.S. market for the same reasons. Where a broad blocking patent exists in Canada, but not in the United States, the impact is greater on Canadian NBFs than on U.S. biotechnology firms because it affects Canadian firms' ability to manufacture the product in Canada to supply both domestic and off-shore markets. Where a broad blocking patent exists in the United States, but not in Canada, the impact of such a patent is about the same on Canadian and U.S. biotechnology firms because both are denied entry into the large U.S. market.

A biotechnology firm which is considering R&D or commercializing a product or process covered by a broad blocking patent must either be willing to assume the risk of being sued for patent infringement or obtain a licence under the blocking patent from the patent owner. In this way, the patent itself becomes a source of revenue without the necessity of commercial activity by the patent holder.

Under Canada's *Patent Act* and regulations, a patent application is deemed to be abandoned if an applicant does not request its examination within seven years of the date of filing or within seven years of the priority date of the application. The purpose of this legislation is to prevent an applicant from indefinitely maintaining a patent application without having it examined on its merits. Practitioners expressed concern about the number of

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[277] Zahralddin, R. "Note: The Effect of Broads Patent Scope on the Competitiveness of United States Industry." *Delaware Journal of Corporate Law*, Vol. 17, 1992, p. 949; Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Greenfield, M.S. "Notes - Recombinant DNA Technology: A Science Struggling with the Patent Law." *Stanford Law Review*. Vol. 44, 1992, p. 1051

[278] Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1

biotechnology patent applications pending at CIPO with broad claims and for which applicants had not requested examination. The claims contained in the patent application can be quite broad and, if the application is not undergoing examination, the applicant need not restrict the claims. One practitioner gave an example where a multinational refused to invest in a Canadian NBF because of the numerous patent applications pending which contained broad claims, and for which examination had not been requested. The multinational described the situation as a time bomb.

Filing patent applications containing broad claims and *not* requesting examination of such applications may be done for several reasons:

- applicants wish to determine the scope of claims granted by other patent offices before requesting examination before CIPO ;
- such applications may prevent competitive biotechnology companies from manufacturing, using or selling biotechnology products or using biotechnology processes covered by those claims;
- such claims are likely to be restricted during examination;
- such claims are not patentable; and
- such patent applications will assist in raising capital.

To avoid broad blocking patent applications, one practitioner suggested that the *Patent Act* be amended to require that requests for examination be made within a shorter period than seven years from the filing or priority date. Another practitioner suggested that the *Patent Act* be amended to abolish requests for examination so that all applications undergo examination immediately.

Under Canada's patent legislation, patents are presumed to be valid, unless they are held invalid by a court of competent jurisdiction. Once broad blocking patents are issued, the owners of such patents have the right to prevent other persons from making, using or selling products and processes claimed in the patent. The owners may simply request in writing the cessation of manufacture, use or sale of biotechnology products; or the use of biotechnology processes. Or they may sue for patent infringement. Even with a legal opinion that a patent is likely invalid, biotechnology firms (particularly small NBFs) are often unwilling to assume the risk of litigation by conducting R&D or commercializing a product or process covered by a broad blocking patent.[279] Canada's 10 percent market (compared to the U.S. market) often does not justify an investment of $100,000 to $500,000 (not counting appeal costs) and the time to manage the litigation of IP issues. The small market size conditions *all* investment decisions in Canadian biotechnology and, in and of itself, becomes a

[279] Greenlee, L.L. "Biotechnology Patent Law: Perspective of the First Seventeen Years, Prospectives of the Next Seventeen Years." *Denver University Law Review*. Vol. 68, 1991, No.127-140, p.134.

competitive disadvantage when Canadian NBF products compete with those of biotechnology firms with larger home markets.

The firms most likely to litigate IP rights or to challenge decisions of CIPO are multinational firms. These firms are willing to invest the capital to litigate when the issue is sufficiently important to them and when the market size justifies the cost of litigation.

Certain large biotechnology firms adopt strategies which include aggressively suing other companies for patent infringement.[280] Successful litigation is a source of capital for such firms. However, by defending litigation, biotechnology firms incur immense costs which divert the resources of management and inventors of companies, retard the pace of development and reflect socially and economically unproductive activity.[281] Thus, few biotechnology firms are willing to assume the risk of infringing broad blocking patents.

When biotechnology firms defer seeking advice on infringement until late in product development, they may learn that broad blocking patents could impede commercialization. In such situations, biotechnology firms tend to seek licences, form strategic alliances or alter their strategy of product development.

In many cases, the owner of a broad blocking patent may be unwilling to license another person to make, use or sell products or processes claimed in the patent: Amgen is an example.[282] Thus, when a biotechnology firm wishes to avoid the risk of being sued for patent infringement and when the patent owner refuses to license the firm to use the patent, the only course available to the biotechnology firm is to refrain from manufacturing, using or selling products, or from using processes claimed in the patent.

In the pharmaceutical industry, certain patent offices tend to grant broad patents on new uses for old products and on isolated and purified forms of naturally occurring products.[283] This is a practice of the U.S. and European patent offices. In certain cases, CIPO has issued broad patents on isolated and purified forms of naturally occurring products if the "core" of the isolated product differs from the "core" of the naturally occurring product. There is support in Canada for granting patents for isolated and purified naturally occurring products (*Continental Soya*).

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280 Zahralddin, R. "Note: The Effect of Broads Patent Scope on the Competitiveness of United States Industry." *Delaware Journal of Corporate Law*, Vol. 17, 1992, p. 949; Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Greenfield, M.S. "Notes - Recombinant DNA Technology: A Science Struggling with the Patent Law." *Stanford Law Review*. Vol. 44, 1992, p. 1051

281 Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1

282 Ibid

283 Ibid

Other practitioners proposed that patent offices restrict the claims in patents granted for biotechnology products to process claims.[284] This proposal reflects the reality that courts considering infringement of broad product claims tend to find infringement only when the product was made by the process described in the patent.[77]

Process claims include "the use of a biotechnology product for a particular purpose" or "a process of isolating and purifying a naturally occurring biotechnology product for a particular purpose." These types of claims give no person the right to restrain *all* manufacture, use and sale of the product. Rather, it only gives a person the right to restrain manufacture, use or sale of a product made by the claimed process. Therefore, such claims create limited rather than broad barriers to economic development in that the patent owner only has the right to restrain others from carrying out a method of manufacture or a method of using a biotechnology product. Other persons can engineer around such restricted claims and develop their own method of manufacture or method of using a biotechnology product. Restricted claims would allow technical advancement in biotechnology to proceed while broad claims impede advancement.[285] Also, it is worth noting that it is more difficult to establish that a patented process has been infringed than it is to establish infringement on a product patent.

The difficulty with only awarding process or method claims is that the patent offices of most industrialized countries grant broad blocking patents on pioneer products of biotechnology. Such offices do not restrict allowable claims to process claims. Thus, if Canada wishes to harmonize its policies with those of other industrialized countries, it will have to convince other countries to change their practice or be willing to grant claims of similar scope to those granted by other patent offices. On the other hand, the government could decide on a "made in Canada" policy to stimulate resident Canadian biotechnology firms and provide consumers with a wide range of biotechnology products at reasonable prices. If the federal government reached this decision, it could decide that, as a matter of national interest, product claims be restricted to the processes for preparing the products. The restriction of patentees to process-dependent product protection for biotechnology products may, however, be contrary to Canada's obligations under GATT and NAFTA. Since U.S., European and Japanese markets are important for successfully commercialized Canadian biotechnology products, export considerations may also affect Canada's flexibility in developing a substantially different patent regime.

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[284] Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Greenfield, M.S. "Notes - Recombinant DNA Technology: A Science Struggling with the Patent Law." *Stanford Law Review*. Vol. 44, 1992, p. 1051

[285] Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1

Another potential option would be for patent offices to require applicants to restrict the claims in patent applications to the genotype or "fingerprint" of the product.[286] The genotype is the genetic information that is unique to the product or lifeform. Applicants who wish to broaden their patent coverage would be forced to link parts of the gene to a desired phenotypic trait. Research would be directed toward identifying specific genes responsible for such traits and would remain competitive due to the inability of the original patent owner to exclude others from patenting other genotypes. Kingwell proposes that we learn from the chemical patent practice when a patent office has required applicants to restrict their claims to "fingerprint" claims which describe the invention.[287] However, this approach has the same drawbacks outlined above. Canada would be out of step with other patent offices if it were to adopt this approach. A further approach is to require applicants to limit claims to a structure–function relationship so applicants describe the product's sequence, proposed function and ability to perform that function.[288]

Uncertainty of patent scope. Most interviewees considered delays in obtaining patent protection and uncertainty in the scope of patent protection as hindrances to the ability of Canadian NBFs to raise capital. Significantly, most IP practitioners and members of the Canadian biotechnology industry indicated that Canada's IP protection for biotechnology inventions, in certain instances, does act as a barrier to the commercialization of biotechnology products in Canada and to the global commercial success of Canadian NBFs.

These practitioners noted that deferring publication of policies until courts decide the issues is an inadequate approach. First, only biotechnology firms with large capital resources will bring their issues to the courts. Second, the courts take many years to decide such issues (taking appeals into account). Third, if patent offices were continually to defer making policy until courts reached decisions, uncertainty about the scope of IP protection would increase. This uncertainty would increase the cost of capital for Canadian NBFs. Fourth, courts decide issues based on the particular facts in a given situation and, as a result, are ineffective policy makers.

Interviews revealed that Canada lacks published policies on a number of important issues affecting biotechnology inventions. Lack of policies has resulted in Canadian patents having claims of inconsistent scope. Practitioners gave a number of examples. One example relates to claims to rDNA products which have different structures than natural products, but which may have a similar "core" to the natural products. In certain cases, isolated and purified products, and rDNA products which resemble, but are different from, their natural counterparts are patentable provided that such products are new, useful and non-obvious. However, CIPO refuses to grant claims for these products when their "core" is the same as

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286 Kingwell, B.G. "Functional Language and Fingerprints." *Canadian Intellectual Property Review.* Vol. 10, 1993, p. 87.

287 Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1

288 Collard, C. "Limited Patent Protection for Proteins." *Canadian Intellectual Property Review.* Vol. 10, September 1993, p. 25.

the natural product. When applicants can demonstrate that the "core" of the rDNA product is different from the natural product, these practitioners argued that CIPO should grant claims to the rDNA product. These practitioners were unaware of this practice in any patent office other than CIPO. This has resulted in claims of different scope for similar products covered by Canadian patents and for identical products covered by patents of different countries.

Another example related to claims to "methods of medical treatment." This type of claim is drafted in the format of a "method of treating (a particular disease or condition) using (a medicine)." Except in certain instances (described above in Section 6.1.2 on the discovery of biologically useful properties in a substance already known in itself, which identifies pre-1992 CIPO decisions granting protection for new therapeutic uses of known compounds), CIPO had refused to issue claims to methods of medical treatment relying on the Supreme Court of Canada's decision in *Tennessee Eastman Co. v. Commissioner of Patents* and on the Federal Court of Appeal's decision in *Imperial Chemical Industries Ltd. v. Commissioner of Patents*. However, beginning in 1992, CIPO accepted claims to "the use of a medicine to treat mammalians." CIPO has not published a written policy on this change and the validity of such claims is in dispute.[289]

Another example concerns the application of sub-section 39(1) of Canada's *Patent Act* (discussed above in Section 6.3.1 under process-based patents) which provided protection for process-specific claims. Despite the existence of this sub-section, CIPO has granted product claims to interleukin-2 and to GM-CSF,[290] although such products were prepared by microbiological processes. In other cases, CIPO has refused to issue product per se claims. A subsequent check with CIPO revealed, however, that interleukin-2 was a chemical, and not a microbiological, case.

IP practitioners point to claims of an inconsistent scope for Canadian patents and claims of an inconsistent scope for Canadian patents and corresponding foreign patents, to illustrate that the policies of CIPO affecting biotechnology inventions are unclear or conflict with those of patent offices of other industrialized countries. This creates uncertainty in the scope of IP protection available for biotechnology inventions in Canada. During interviews, practitioners recommended that CIPO create and publish policies on the patentability of biotechnology inventions through open consultations with practitioners. Of course, it is not clear whether these IP practitioners would invite truly open consultations involving all members of the public.

Opposition process to challenge issued patents. A leading spokesperson for Canadian NBFs suggested an "opposition" appeal process at CIPO which would allow applications for broad blocking patents to be challenged within some review period (e.g., nine months) and at small cost (see text on broad blocking patents, this chapter). This would give small NBFs

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289 Britt, K.R. "Method of Use Claims in Biotechnology." *Canadian Intellectual Property Review*. Vol. 10, 1993, p. 101.

290 Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." C.I.P.R, Vol.10, 1993, p. 347

with competing, but more specific technologies, the opportunity to object to broad blocking patents of large multinationals in an expeditious and relatively inexpensive way. This appeal mechanism exists in the European Patent Office.

Process-based patents. Interviews indicated that Canadian NBFs tend to seek patents on their products rather than on their processes. However, interviews with practitioners suggested that this strategy is changing and that firms are exploring the option of patenting their processes as well as their products of manufacturing.

Before 1987, the *Patent Act* prohibited product per se claims (i.e., claims to a product independent of its process of manufacture) for inventions relating to substances prepared or produced by chemical processes and intended for food or medicine. A patent applicant could only claim a product as made by a particular process (process-dependent product claims). The process had to be claimed as well as described, otherwise there could be no claim for the product. Since biotech products may be produced by different processes, the prohibition on product per se claims encouraged competitors to develop alternative processes in order to make competing non-infringing versions of biotech products.

In 1987, the *Patent Act* was amended to restrict this prohibition on food and medicine product per se patents to only those inventions relating to naturally occurring substances made by *microbiological processes* and intended for food or medicine. This amendment [section 39(1) of the *Patent Act* shown below] provided some IP protection to the Canadian biotechnology industry. It came into force on November 19, 1987 and ceased to have effect four years later on November 19, 1991.

> 39(1) In the case of inventions relating to naturally occurring substances prepared or produced by, or significantly derived from, microbiological processes and intended for food or medicine, the specification shall not include claims for the resulting food or medicine itself, except when prepared or produced by or significantly derived from the methods or processes of manufacture particularly described and claimed.

There has been an ongoing dispute since 1987 as to how to interpret this provision.

Between November 19, 1987 and November 19, 1991, CIPO did not grant any patents containing product per se claims covered by the new narrower prohibition. However, CIPO continued to apply section 39(1) to reject product per se claims for patent *applications filed before October 1, 1989 and still pending on November 19, 1991.* This practice was widely criticized by multinational enterprises which believed that their patent applications filed before October 1, 1989 for naturally occurring products made by microbiological processes and intended for food or medicine, and pending on November 19, 1991 should be allowed to contain claims to the substances without any process limitations

CIPO's practice in this regard has recently been overturned. In a decision of the Patent Appeal Board on January 13, 1995, it was held that CIPO's practice with respect to section 39(1) was based on an apparent misinterpretation of the *Patent Act,* and the "sunsetting" of section 39(1) on November 19, 1991 was applicable to all patent applications. Consequently, any patent pending on November 19, 1991, *regardless of when filed,* would now be allowed to contain product per se claims to substances made by microbiological processes and intended for food or medicine, without any process-dependent product claim restrictions.

During interviews, certain IP practitioners remarked that CIPO's practice (before the January 1995 Patent Appeal Board decision) was correct with regard to the transitional provisions of Canada's *Patent Act.* Other practitioners questioned its correctness as the sub-section ceased to have effect in November 1991. These practitioners remarked that a protectionist approach:

- was contrary to NAFTA and GATT;
- encouraged other countries to adopt protectionist measures which would adversely affect Canadian NBFs seeking to sell products in such countries; and
- affected harmonization efforts.

Deposits of biological material. During our interviews, Canadian IP practitioners supported the ongoing work of the government in the area of deposits of biological material, sequence listings and the SUN workstation.

CIPO is drafting regulations for the deposit of biological material. Practitioners criticized Parliament's delay in passing laws recognizing deposits of biological material to support descriptions in patent applications. However, Parliament has passed deposit provisions in its Bill S-17 which will not come into force until regulations are finalized. These practitioners remarked that other industrialized countries have recognized deposits for some time. The United States and Japan signed and ratified the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (1977) on the day it came into force — August 19, 1980. Most European countries had acceded to this treaty by 1987.

Effective Patent Term:

CIPO delays in reviewing patent applications and other policy issues. Most practitioners expressed dissatisfaction with delays in the examination of biotechnology patent applications. When told that CIPO has expedited the issuance of first office actions on the merits of applications, most practitioners remarked that they had not noticed this and were eager to see whether CIPO will expedite the issuance of second and third office actions.

A practitioner for the generic drug industry noted that, of some 26,000 patents filed each year in Canada, fewer than 5 percent are Canadian in origin. He recalled that, as of three or four years ago, there were about 700 or 800 pharmaceutical patents pending. He noted the drug, Enalapril, as a good example of a patent delay issue. A patent for the drug was

first filed in the United States in 1978 and issued in 1984. Merck & Co. Inc. obtained a Canadian patent for Enalapril on October 16, 1990.

There is a negative trend in the "efficiency" of biotechnology patent examiners due to the rising complexity of applications, the increasing size of the literature search and the increasing attention paid to the scope of patents.[291] According to certain authors, backlogs in patent applications seriously impede the development of technology while the applications remain in limbo.[292] Backlogs act as a serious economic burden for small biotechnology firms.[293] Interviews with practitioners confirm these findings.

The November 1991 report of the National Biotechnology Advisory Committee concluded that delays in the prosecution of biotechnology patent applications are discouraging new research and investments in commercial facilities, driving up the costs of innovation and undermining public confidence in biotechnology.[294]

Since 1991, CIPO has made a concerted effort to reduce the backlog of biotechnology patent applications by hiring more examiners (bringing the total number of examiners to nine). In the short term, this may increase the backlog due to the training time that senior biotechnology examiners must invest in training new biotechnology examiners.

Practitioners also voiced concerns with the delays in patent prosecution, conflict proceedings and Patent Appeal Board hearings relating to biotechnology inventions. One practitioner used the example of a biotechnology patent application which has been pending for more than 13 years and which is still undergoing prosecution in Canada. In the meantime, patents for this invention have been issued in the United States and Europe.

Practitioners we interviewed stated that delays and protracted prosecution are costly, especially to small biotechnology firms. They act as barriers to the commercial success of Canadian biotechnology companies.[295] Delays also impede the ability of biotechnology firms to extract capital from their biotechnology patents via licensing, distribution, sale or joint venture agreements. Delays and the cost of protracted prosecution cause many small biotechnology firms to either abandon their IP protection or concede on their scope of rights

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[291] Griliches, Z. *Patents: Recent Trends and Puzzles.* In Brookings Papers: Microeconomics, The Brookings Institute, 1989.

[292] Breyer, N. "Japan's Patent System." *Journal of the American Chamber of Commerce in Japan*, 1988, p. 16; Greenlee, L.L. "Biotechnology Patent Law: Perspective of the First Seventeen Years, Prospectives of the Next Seventeen Years." *Denver University Law Review.* Vol. 68, 1991, No.127-140, p.134.

[293] Ibid

[294] National Biotechnology Advisory Committee. *National Biotechnology Business Strategy: Capturing Competitive Advantage for Canada.* 5th Report, Industry, Science and Technology Canada, 1991.

[295] Greenlee, L.L. "Biotechnology Patent Law: Perspective of the First Seventeen Years, Prospectives of the Next Seventeen Years." *Denver University Law Review.* Vol. 68, 1991, No.127-140, p.134.

in order to obtain issued IP protection.

Reducing delays in granting patents at CIPO must be accompanied by a decrease in regulatory approval delays because issued patents are only valuable once approval to sell the product is granted.

Patent filing first in other countries. Canadian NBFs tend to seek IP protection for their inventions first in countries other than Canada, most often in the United States (Table 6.5). In contrast, foreign NBFs tend to file patent applications first in their home countries. An earlier report concluded that Canadians rank low in their propensity to file patent applications outside of Canada.[296]

Canadian NBFs follow this patent strategy of seeking IP protection first in the United States because:

- the United States is a major market and it is more important to obtain IP protection in the United States than in Canada;
- the USPTO is more likely to issue a first action on the merits of the application before CIPO would (even if an applicant files in Canada and requests examination immediately); and
- the United States allows applicants to add new matter to the patent application as R&D progresses by filing continuation-in-part (CIP) patent applications.

However, the USPTO plans to revise its patent legislation to make the length of a patent term 20 years from the date the first *complete* application is filed (currently the term of a patent is 17 years from the date granted in the United States). The revision is intended to prevent patent owners from using CIPs or divisionals to maintain a monopoly on technology decades after the first filing of their application. Also, the extension of the U.S. patent term from 17 years from the date of issue to 20 years from the date of filing is a requirement of the GATT–TRIP agreements (article 33 of TRIP) that must be implemented by every member.

Canada is a small market compared to the United States and the European Union. To be successful, Canadian NBFs must be able to enter into and compete in global markets such as the United States, Europe, Japan, Korea, Australia and New Zealand. IP protection in these countries is crucial to the profitability of Canadian NBFs without which they would:

- be locked out of international markets;
- lose bargaining power with owners of broad blocking patents; and
- risk having competitors copy their biotechnology inventions.

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296 French, D.J. "Foreign Patenting by Canadians." *World Patent Information*, Vol. 9, 1987, p. 10.

Erosion of effective patent term. Members of Canadian NBFs indicated that increased regulatory control of biotechnology products delays market entry of products and erodes the effective patent term. Canada is now moving to regulate previously unregulated biotechnology product areas. For instance, in August 1992, Health Canada published an Information Letter on the proposed regulation of novel foods and, in October 1994, published *Draft Guidelines for the Safety Assessment of Novel Foods.* The proposed regulations and guidelines would require manufacturers of foods produced using rDNA technology to notify Health Canada before marketing these foods. Health Canada would then assess the marketing of such foods.

Also, in October 1992, Environment Canada published its draft regulations for biotechnology products under the *Canadian Environmental Protection Act* (CEPA). According to the proposed regulations, all biotechnology products will be subject to the standards of safety established by the CEPA regulation before their importation, manufacture or use in Canada (see Chapter 5).

The *Federal Regulatory Plan 1994* described many other areas affecting biotechnology products in which the federal government proposes to increase regulation. In fairness, we have to add that these proposed regulations were prepared in recognition of the fact that applications for approval to market recombinant food products in Canada were forthcoming. Also, it was necessary to prepare appropriate regulations to safeguard the environment, particularly the semi-contained and open release of rDNA products (in agbio and environmental applications) given that such products were fast approaching the regulatory approval stage. Consequently, while it is true that effective patent terms are eroded by prolonged regulatory review, the issue has not been critical to the development of Canadian biotechnology firms. The views decrying regulatory control arose among certain IP practitioners.

NAFTA recognizes that it may be appropriate in certain instances to extend the term of a patent. Paragraph 12 of article 1709 of NAFTA provides that a party "may extend the term of patent protection, in appropriate cases, to compensate for delays caused by regulatory approval processes." Although NAFTA recognizes patent term extension, it is not currently available in Canada under the *Patent Act.*

Patent term restoration has been implemented in the United States, Europe and Japan.[297] In view of the increased regulation proposed for biotechnology products and processes, Canadian biotechnology firms would benefit from a change to Canada's laws to provide for patent term restoration.

Compulsory licensing. It is not surprising that generic drug industry representatives called for the re-establishment of compulsory licensing under the pre-Bill C-22 environment. An IP practitioner for this industry suggested that it didn't achieve any noteworthy advantages. For example, the seven to 10-year provision in Bill C-22 provided some inducement for the

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[297] Redwood, H. *Pharmaceutical Patent Restoration for the 1990s: An international enquiry into cause and effect.* Oldwicks Press, 1989.

development of a Canadian fine chemical industry, but this advantage, in his opinion, had been eroded by the globalization effects of GATT. Canadian generic drug companies are effectively blocked from getting into the markets of other countries under GATT since patents expire in Canada after the priority filing country (often the United States). He also noted that, were it not for the issuance under U.S. judicial order of compulsory licences for such things as computer chips and colour televisions, Japan would never have been able to get its own computer industry off the ground. The same was true, in his opinion, for Bell Labs in the United States.

Organizations representing consumers' interests wanted to ensure that Canadian consumers have a selection of different biopharmaceutical (and pharmaceutical) products at reasonable prices. Their views can be summarized as follows:

1. Canada should have compulsory licensing of patented medicines including patented biopharmaceuticals.

2. Bills C-22 and C-91 harmed consumers' interests in that they failed to control the pricing of patented medicines.

3. The generic drug industry helps give Canadian consumers a selection of drugs at reasonable prices.

Consumer organizations filed memoranda with the federal government during the Bill C-91 hearings. Their spokespersons indicated that their current views were substantially unchanged. They noted that the PMPRB has been ineffective in ensuring that the pricing of patented medicines is not excessive. In regard to the apparent lack of control of patented medicine prices under bills C-22 and C-91, the PMPRB has verified that the *factory gate prices* of patented medicines have risen by less than the Consumer Price Index during the period following passage of Bill C-22. However, the dispensing fees for these medicines have increased enormously during the same period which accounts for the overall above-inflation increases in pricing. These price increases cannot be attributed, therefore, to the *Patent Act*.

Consumer groups also noted that some biotechnology firms circumvent the jurisdiction of the PMPRB by dedicating Canadian patents on biopharmaceuticals to the public. In this regard, the PMPRB recently announced a proposal that would preclude patentees from avoiding the Board's price review authority by dedicating a patent. Stakeholders were invited to comment on this proposal by May 1, 1995.

Spokespersons for some Canadian NBFs and subsidiaries of multinationals indicated that amendments to the *Patent Act* to abolish compulsory licensing of patented medicines have induced increased R&D investments in Canada. For instance, one leading Canadian NBF enjoyed a significant infusion of capital as a direct result of these changes. A 1991 report concluded that Canada's then existing IP laws may have adversely affected the ability of Canadian-owned firms and foreign subsidiaries to attract capital and therefore affected the

level of innovation in Canada.[298] However, this report was prepared before Canada's patent laws were changed to abolish compulsory licensing for patented medicines.

Some authors have argued that the delay in abolishing compulsory licensing in Canada has acted as a historical disincentive to market entry for NBFs.[299]

As noted in Section 6.1.5, the re-establishment of a drug patent compulsory licensing regime would be contrary to Canada's international obligations under the GATT–TRIP agreements and NAFTA. J.G. Castel, Professor of International Business Law at Osgoode Hall Law School (York University), has provided a legal opinion indicating that Canada was not obliged to eliminate compulsory pharmaceutical patent licensing under either GATT or NAFTA.[300] He contended that this was because the compulsory licensing regime could be brought under the "limited exceptions" provisions of GATT–TRIPs (article 30) and NAFTA [article 1709(6)], which provide that "members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties." However, the government's position has been that sector-specific compulsory licensing provisions do not fall under the rubric of "limited exceptions" and are governed by NAFTA article 1709(10) and GATT–TRIPs article 31 ("Other Use Without Authorization of the Right Holder") which sets out the conditions of use of a patented invention without authorization of the right holder. This interpretation is consistent with the negotiating history of the GATT–TRIPs agreement and NAFTA texts.

Additionally, the re-establishment of compulsory licensing would have to be considered in the light of broader trade and industrial policy issues. For example, the brand name pharmaceutical industry in this country has made a voluntary commitment to invest in Canadian R&D at a level of 10 percent of its annual value of sales. Furthermore, there would undoubtedly be reactions from the international community should this regime be restored.

PMPRB and patent dedication issue. Certain practitioners commented that the PMPRB acts as a barrier to investment in biopharmaceutical development in Canada. This is due to the extensive filing requirements coupled with the strong remedies that the PMPRB can order

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[298] Langford, J. and D. Blaker. "The role of intellectual property in the competitiveness of the pharmaceutical sector." *1991 Pharmaceutical Review.* Intellectual Property Review Branch, Consumer and Corporate Affairs Canada, October 1991; Kaminski, K.T. "Disclosure of Information in a Computer-Readable Form for Biotechnology Inventions." *Canadian Intellectual Property Review.* Vol. 10, September 1993, p. 93.

[299] Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review.* Vol.10, September 1993, p. 145; Duncan, H.S. "Canadian Biotechnology Patents - An Industry Perspective." C.I.P.R, Vol.10, 1993, p. 347.

[300] Castel, Prof. J.G. *Legal Opinion with respect to Canada's Intellectual Property Obligations regarding pharmaceutical patent licensing under the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Agreement (NAFTA).* Canadian Drug Manufacturers Association, Toronto, March 23, 1993.

if it considers pricing of patented medicines to be excessive.

The PMPRB's filing requirements include semi-annual statements of sales and prices for patented medicines sold in Canada. The Board reviews the average prices from sales for the six-month periods January 1 to June 30 and July 1 to December 31. It considers the following factors in determining whether the reported price of a patented medicine is excessive:

- the price of the medicine in the previous five years;
- the prices of other medicines in the same therapeutic class;
- the prices of those medicines in other countries; and
- the Consumer Price Index.

When the Board determines that a patented medicine is being sold in Canada at an excessive price, the PMPRB can:

- request reduction in the price of the medicine;
- request reduction in the price of another patented medicine of the patent owner;
- remove the patent owner's exclusive right to sell the medicine or other patented medicines in Canada; and
- impose fines.

In its September 1989 bulletin, the PMPRB published comments on "Supplementary Guidelines: Excessive Price." In their submissions, pharmaceutical industry representatives remarked that the guidelines extended the PMPRB's functions from price review to price control. "Some patentees questioned whether they would now be willing to increase or maintain their level of research and development in Canada should these guidelines remain in force. Additionally, some patentees questioned whether they would now be willing to introduce new medicines in Canada given the restrictive nature of the supplementary guidelines."

While the *Patent Act* contains no provision as to the dedication of a patent, it is well settled that patent rights may become abandoned through the dedication of a patent to the public. To circumvent the jurisdiction of the PMPRB (which has published a policy on the issue), a number of firms have dedicated their patents on medicines to the public.[301] The existence of a patent application and a patent deters, if not prevents, competitors from market entry prior to patent expiry, and the dedication often takes place once a firm has established its exclusive market position. In such circumstances, dedicating the patent to the public has no adverse effect on the firm because of the long lead time a competitor would need to develop a manufacturing capability and regulatory approval for the biopharmaceutical. And Canada's small market size also acts in this instance as a barrier to competition as well. Yet

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[301] Marusyk, R. and M. Swain. "Price Control of Patented Medicines in Canada." *Canadian Intellectual Property Review.* Vol.10, September 1993; Horton, J. "Pharmaceuticals, Patents and Bill C-91: The Historical Perspective." *Canadian Intellectual Property Review.* Vol.10, September 1993, p. 145

dedicating the patent to the public circumvents the jurisdiction of the PMPRB and restores the firm's ability to control the pricing of its product

Recently, the PMPRB proposed to change its current price review practice in the case of patents which are surrendered for public use in order to assert its jurisdiction after a patent has been dedicated.[302] The proposal is intended to prevent patentees from avoiding the jurisdiction of the PMPRB by surrendering their patent rights. In six of the 10 voluntary compliance undertakings (VCUs) approved by the Board since 1993, patentees dedicated their patents and did not lower prices to comply with the PMPRB's price guidelines.

The Board's current practice is to cease reviewing the price of a patented medicine on the dedication of the relevant patents pertaining to it. Although the term "patent dedication" is not recognized in the *Patent Act*, the practice of dedication which has evolved consists of the patentee notifying the Commissioner of Patents that it has surrendered its rights and entitlements flowing from the patent for the benefit of the public to sue and enjoy. The Board has noted that:

> Bill C-91...established a new regime to facilitate the entry of competitors immediately upon the expiry of a patent, to stockpile and seek regulatory approval of products prior to the expiry of a patent. At the same time, subsection 55.2(4) provides for strengthened protection for pharmaceutical patentees with the establishment of a patent register by Health Canada; the policy is to ensure that Health Canada does not approve a drug for sale when such a sale would infringe a valid patent. These amendments appear to have been designed to ensure patentees enjoy the benefits of their statutory rights during the normal patent term, but not beyond it.
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> With these principles in mind, the legislation should be interpreted in a manner that best ensures the attainment of its objectives.
>
> While patent dedication may end a patentee's ability to enforce its exclusive rights through an infringement action (although this has never been judicially determined) it will not, in most cases, immediately remove benefits accruing indirectly from the patent because of delays involved in entry by competitors.
>
> Potential competitors know when a patent will expire but they cannot anticipate patent dedications. When dedication occurs, development work, product testing and the approval process would likely commence only after the dedication became known. It can take a few years to develop, and obtain regulatory approval for a competing version of a drug product. Under the Board's current practice, the effect of patent dedication may be to allow the dedicating patentee a substantial opportunity to enjoy the benefits of the

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[302] Patented Medicine Prices Review Board. "Dedicated Patent - Notice and Comments." *PMPRB Bulletin*, Issue No. 15, January 1995, pp. 5-8.

patent while avoiding price regulation.

> In view of the foregoing, the Board believes that the proper interpretation of "patentee," as defined in section 79, includes a patentee in the post-dedication period. The Board is of the view that a dedicating patentee continues to be "entitled to the benefit of the patent" beyond the date of the patent surrender.

Interested parties were invited to comment on the proposal by May 1, 1995. The Board sought input from ministries of health, representatives of consumer groups and the pharmaceutical industry, and other stakeholders including the Patent and Trademark Institute. Comments from all concerned will be carefully considered by the Board before any decision is made on its proposal.

Patent Infringement Issues:

Section 55.2 issues. A generic drug industry spokesperson pointed out a growing problem concerning patent-delaying tactics related to the section 55.2 amendment to the *Patent Act* under Bill C-91. Some background explanation is in order to understand the issue. In February 1993, the *Patent Act Amendment Act*, 1992 (Bill C-91), with the exception of section 55.2, received royal assent. In March 1993, section 55.2 [with an amendment, section 55.2(4), which was added to Bill C-91 at third reading] was proclaimed as was the Patented Medicines (Notice of Compliance) Regulations pursuant to the authority set out in section 55.2(4) of the Act. Bill C-91 abolished the system of compulsory licences for patented medicines which had existed in Canada in various forms since 1923. Furthermore, as of February 15, 1993, it abolished all compulsory licences granted on or after December 20, 1991. Only those compulsory licences granted before December 20, 1991 were to continue in effect according to their terms and were to be governed by the otherwise repealed provisions of the *Patent Act.*

One of the other significant features of Bill C-91 was section 55.2 which provides certain defences to patent infringement actions for persons who use patented inventions in order to develop information that is required as part of a regulatory approval process, or who manufacture and store patented articles for sale after the expiry of applicable patents. In other words, the amendments had a balanced intent for the generic drug industry. On the one hand, they abolished compulsory licensing, while on the other, they permitted the sale of generic equivalents of patented medicines immediately on patent expiration.

Section 55.2 also confers on the Governor in Council the authority to make regulations to prevent patent infringement by anyone who deals with a patented article "in accordance with subsection (1) or (2)." The regulations associated with section 55.2(1) prevent the Minister of Health from issuing a notice of compliance (NOC), as required to market the product, to a generic drug manufacturer when there is any challenge under the regulations over patent rights to the pharmaceutical in question.

More specifically, the Patented Medicines (Notice of Compliance) Regulations, SOR/93-133, allow a patent holder to obtain an order prohibiting the Minister of Health from issuing an NOC to a generic pharmaceutical company until after the expiration of the patent in issue. The regulations establish the following process.

1. To benefit from the regulations, patent holders seeking an NOC for their products have to disclose all relevant patents and expiry dates they believe apply to their products;

2. When generics seek an NOC for a copy of any such products, they must indicate whether or not they accept that the NOC should not issue until the patent expiry date set out by the earlier (patent-holder) applicant;

3. If the generic agrees to wait until patent expiry, the NOC will be made available no earlier than that date;

4. If the generic disagrees with the date, it will notify the patentee. The patentee then has 45 days to initiate court proceedings to prevent the Minister of Health from issuing the NOC before the expiry of the contested patent;

5. The NOC cannot be granted for up to 30 months after the start of the court action unless the patent expires earlier, the court case is resolved earlier, or the court decides to shorten or lengthen the 30 month period;

6. Should a generic succeed in the court action, the court has authority to award damages against a patentee to compensate the generic for its lost market opportunity.

It was one IP practitioner's view that the regulations are discriminatory and arguably violate Canada's GATT and NAFTA obligations. Furthermore, they are unjust because they grant what is, in effect, an injunction without a court having determined that such an injunction is warranted by the facts of the case. A challenge to the validity of the regulations is before the courts.

According to this practitioner, the regulations set up a situation permitting the holder of a drug patent to extend its effective term or period of exclusivity for years beyond the patent's termination date. In a legal opinion, Professor Patrick Monahan of Osgoode Hall Law School,[303] noted that the NOC regulations parallel, approximately, comparable

[303] Monahan, Prof. P.J. *Legal Opinion re: The validity of the Patented Medicines (Notice of Compliance) Regulations.* Prof. P.J. Monahan, Director, York University Centre for Public Law and Public Policy, Osgoode Hall Law School, August 30, 1993.

provisions contained in the U.S. *Drug Price Competition and Patent Term Restoration Act* of 1984. Monahan contacted a government official who confirmed that, in fact, the NOC regulations were modelled on the 1984 American statutory provisions.

The U.S. legislation represented a compromise between the Pharmaceutical Manufacturers' Association (PMA) and the U.S. generic drug industry. On the one hand, it streamlined the approval process for generic drugs to less than six months. On the other hand, the U.S. legislation extended the 17-year patent term in that country for up to five years on certain products subject to FDA premarket approval. Monahan noted that there is no comparable provision for streamlining approval of generic drugs in Canada. Currently, it takes 42 months, on average, for a generic new drug application to be approved in Canada. He was puzzled by the fact that the regulations appear superfluous in contemplating a 30-month delay in a process where approvals currently take at least that long. Monahan noted, however, that the delay caused by the NOC regulations for applications in the pipeline that were at or near the point of regulatory approval by March 1993 (the proclamation date for the regulations) could be quite extensive. He argued further that these pipeline applications fall outside the scope of authority of the *Patent Act*.

Monahan noted that, while the 1984 American provisions were set out in statute and enacted by Congress, the NOC regulations in Canada were approved by the Governor in Council (i.e., by executive order). In his opinion, the NOC regulations fall outside of the regulation-making authority conferred on the Governor in Council under section 55.2 of the *Patent Act*.

Monahan also noted that draft regulations are normally prepublished in the *Canada Gazette* to permit "full and early consultation with all interested parties" and to ensure "consideration of the potential impact of, and alternatives to, regulation." The Gazette prepublication is to be accompanied by a regulatory impact analysis statement (RIAS), which is to describe clearly the regulation, set out technical and policy alternatives and explain why they were rejected, and identify anticipated impacts, benefits and costs. However, the NOC regulations were not prepublished in the *Canada Gazette* before their enactment by Cabinet. The RIAS accompanying the NOC regulations explains that "given the importance of quickly giving effect to the new statute, consultations have not been undertaken on the text of these regulations prior to their coming into force." The RIAS did not offer any explanation of the urgency in giving effect to section 55.2 as distinct from Bill C-91 as a whole. (Recall that as of March 1993, the remainder of Bill C-91, with the exception of section 55.2, had already been proclaimed.) Exemptions from these requirements can only be extended in a limited number of circumstances. The "cover page" of the RIAS, which is to contain this detailed justification of the reasons for the proposed exemption, was not publicly available, Monahan reported, and was regarded by the government as privileged advice to ministers in July 1993.

The generic drug industry spokesperson noted that there are over 50 challenges currently before the courts delaying the market entry for these generic drug competitors for 30 months or until decisions are reached by the courts. For nearly all the products caught in this litigious net, new drug submissions had already been filed before the regulations came

into force. Arguably, these products were retroactively affected by the change in the law. The spokesperson noted that the cases subject to ministerial injunction were being fought at tremendous expense to the companies involved, to the courts themselves and to the Canadian public to which access to low-priced generics was being delayed. Over several years, these costs were estimated to amount to hundreds of millions of dollars for both loss of sales to the companies and delay of sales to Canadian purchasers of pharmaceutical products.

Although generic biopharmaceutical products have not yet been caught in this litigious net, this issue may have ramifications for Canadian NBFs commercializing therapeutically and biochemically similar (i.e., "me too") biotech products or biotech products using different processes. Under section 55.2, owners of broad blocking patents may be able to challenge these products.

6.3.2 International Developments

Table 6.18 shows some uncertainty in the United States surrounding the application of patent laws to biotechnology. The table also highlights the U.S. lead in the development of biotech patent policy.

The U.S. *Orphan Drug Act* and the U.S. Biotechnology Industry

Congress passed the *Orphan Drug Act* (Public Law 97-414) in 1983, providing strong incentives for pharmaceutical and biotechnology firms to discover and develop treatments for rare diseases and conditions. Amended three times (Public Law 98-551, Public Law 99-91, Public Law 100-290), the Act has three provisions (in addition to a tax credit) designed to subsidize R&D costs or to remove other disincentives to developing drugs of limited commercial value:

- FDA assistance to orphan drug developers in protocol design for new drug approval (NDA) or product licence approval applications;
- research grants for clinical and preclinical studies of orphan products; and
- a grant of seven years of exclusive U.S. marketing rights to the first firm that receives NDA approval for an orphan drug.

The FDA first published proposed regulations to implement the law in January 1991 (FR 1/29/91; 56 FR 3334). The FDA had relied on interim guidelines that differed from the proposed regulations in important ways. Though the proposed regulations have not been adopted officially as final, the FDA has operated under these rules since they were published.[304]

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[304] U.S. Office of Technology Assessment. *Pharmaceutical R&D: Costs, risks and rewards.* USOTA, Report No. OTA-H-522,Washington, DC, February 1993, pp. 225 ff.

- Between January 1984 and the end of September 1992, the FDA granted orphan status to 494 drugs and biologicals. Almost two thirds of orphan designations (63 percent) went to sponsors who were not members of the U.S. PMA.

Because PMA membership is available only to companies marketing an FDA-approved pharmaceutical in the United States, this statistic suggests that a high percentage of all orphan drug research is being sponsored by new (and probably small) firms or other organizations with little previous experience in researching and marketing drugs in the United States. (i.e., NBFs).[305]

The first drug sponsor to receive NDA approval for a drug and indication with orphan status may market it exclusively for a seven-year period beginning on the day the FDA approves the drug. This exclusivity prevents the FDA from approving an NDA for a drug for which another sponsor has already received marketing approval for the same indications. Any patent protection covering the drug runs concurrently with the market exclusivity. Two or more sponsors may receive FDA approval for a single orphan drug if their approvals are for different indications and if they do not violate any patent protections.

In practice, the exclusivity clause is the strongest incentive in the orphan drug legislation. For some drugs, it may be more important than patent protection in effecting market exclusivity. Orphan market exclusivity may extend beyond the expiration of the relevant patents. Because manufacturers usually receive their 17-year patents on potential new drugs early in the development process, the amount of time remaining on the patent at the time of FDA approval may be less than the seven years guaranteed by the orphan drug exclusivity. Some drugs duplicate substances that naturally occur in the body (e.g., biologicals). For these, the state of patent law is currently so murky that the seven-year market exclusivity is a more certain means of protecting the product from competition.

Controversy has arisen over how different the molecular structure of two drugs must be in order for both to receive market exclusivity. Because biological pharmaceuticals tend to have relatively large and complex molecular structures, scientists can alter their make-up slightly without changing their clinical effects. If the U.S. government interprets any small clinically insignificant change as the creation of a "different" orphan drug eligible for its own market exclusivity, it effectively eliminates the incentives of the exclusivity clause for many biotechnology drugs. Since the orphan drug law was enacted, competitors have challenged the exclusivity of two approved orphan drugs by seeking approval of slightly different versions of the same pharmaceuticals.[306]

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305 Ibid

306 Ibid

Human Growth Hormone - In 1985, Genentech received FDA approval and exclusive marketing as an orphan drug for a human growth hormone (HGH) product to treat children whose bodies do not naturally produce enough of the hormone to ensure normal growth. Genentech's HGH product, Protropin™, contains one more amino acid than is found in the version usually produced by the body's pituitary gland, but this particular amino acid does not appear to alter the hormone's activity in the body.

Table 6.18[a]

Sources of Uncertainty in the U.S. Concerning the Application of Patent Laws to Biotechnology

Subject Matter:	
Humans	- USPTO excludes humans from patentability. - Office of Technology Assessment (OTA) currently undertaking major research project on issues related to patenting of human body parts, including human gene sequences.[b]
Animals	- USPTO has only granted nine patents on animals (seven mice, one rabbit and one worm) even though there are approximately 370 patents on animals pending.
Farm animals	- The USPTO has yet to grant a patent on a farm animal.
Treatment for AIDS and other viruses - unofficial USPTO policy against granting patents relating to this subject matter.[c]	
Non-Obviousness:	
rDNA and MAb techniques	- U.S. courts and USPTO are increasingly finding the application of biotechnology techniques to be obvious. The USPTO held hearings on October 17, 1994 on the issue of the standard of non-obviousness in the field of biotechnology.[d]
Utility:	
Human gene sequences	- Although the National Institutes of Health withdrew some of their patent applications on human gene sequences, patent practitioners at the 1994 BioEast Conference suggested that human gene sequences may have utility as probes or as bioinformation.[e]
Transgenic plants	- Evolving USPTO practice is to require field tests on transgenic plants to establish utility.[f]
Therapeutic and pharmaceutical products	- The USPTO held hearings on October 17, 1994 on the issue of the standard of utility of a biotechnological invention. These led to the adoption of examiner guidelines for biotechnology applications, which essentially eliminate the practice of requiring clinical trials to support an asserted therapeutic or pharmaceutical utility of a biotech invention.
Broad Claims:	
General concern about the tendency to grant patents that have claims too broad in scope[h]	
-All non-human mammals	- Harvard mouse patent (USP 4736866), exemplified for mice, claimed for all non-human mammals.
-All transgenic cotton and soybean	- The grant of two patents to Agracetus Co. claiming all cotton transformed genetically modified (e.g., Agracetus patent USP 5159135) has been cancelled by the USPTO.[i] A patent granted to Agracetus on all genetically engineered soybean would still be valid at this date.
Submarine patents	-There is concern that pending USPTO patents with broad claims will surface on their grant to invalidate other biotech patents.
Release of Patent Deposit Samples:	
Given that the release of deposited biological material is not limited on any basis of nationality or place of use, there are ongoing concerns that foreigners will access deposits of U.S. patentees and use copies to infringe biotech patents.[j]	
Ownership of Cell Lines:	
Although a person's claim of ownership in her cell line was rejected by the Supreme Court of California,[k] the U.S. government withdrew its patent application claiming a patent on the cell line of an indigenous Guaymi woman from Panama,[l] in response to international pressures.	
International Litigation:	
There is litigation relating to the same conflicting biotechnology patents ongoing in several countries internationally. However, courts in the United States and Europe do not necessarily come to the same ruling about the validity and infringement of biotech patents so litigation acts as a source of global uncertainty.[m]	

Notes:

[a] This research was compiled by staff in the Intellectual Property Policy Directorate, Industry Canada.

[b] Armitage, R.A. "The emerging U.S. Patent Law for the Protection of Biotechnology Research Results." *European Intellectual Property Review.* Vol. 11, 1989, No. 45-57, p. 49; Merges, R.P. "Uncertainty and the Standard of Patentability." *High Tech Law Journal*, Vol. 7, 1992, p. 1; Love, C.G. "A Survey of Recent Biotechnology and Patents Litigation in the U.S." *US Biotech*, Vol. 9, 1991, p.10.

[c] Bent, S.A. "An Evolving European Case Law: Implications for Protecting Biotechnological Innovations." Paper presented at the *International European Development in Intellectual Property and Regulatory Law Conference*, BioEast '94, January 27, 1994, pp. 8-9.

[d] "Hearing set on Patent Protection for Biotechnological Inventions." *BNA's Patent, Trademark & Copyright Journal*, Vol.48, No.510, pp. 518-523. On obviousness of monoclonal antibody technique, see: *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988); *Ex parte Erlich*, 22 *U.S.P.Q.* (2d) 1463 (Bd. Pat. App. & Int., 1992).

[e] Maebius, S.B. *Novel DNA Sequences and the Utility Requirement: The Human Genome Initiative.* J.P.T.O.S., Vol.74, 1992, pp. 651-658.

[f] Lassen, E. *Bioconference 1994*, Toronto.

[g] "PTO Announces New Biotechnology Guidelines." *BNA's Patent Trademark & Copyright Journal.* 1995, pp. 223-225.

[h] Roberts, Tim. "Broad Claims for Biotechnological Inventions." E.I.P.R., Vol. 9, 1994, p. 371.

[i] PATNEWS: "120894 Patent Office revokes third patent." e-mail posting from Greg AHARONIAN, Internet Patent News Service, December 8, 1994. Mr. Aharonian adds that: "the re-examination was ordered by the Patent Office in April, and the rejection of the claims is not final. All of the claims were rejected on prior art grounds. Agracetus can first appeal to the Patent Office, and if unsuccessful, to the Federal courts. If ultimately unsuccessful, the value of Agracetus is expected to greatly decrease."

[j] Greenlee, L.L. "Biotechnology Patent Law: Perspective of the First Seventeen Years, Prospectives of the Next Seventeen Years." *Denver University Law Review.* Vol. 68, 1991, No.127-140, p.134.

[k] *Moore v. Regents of University of California*, 15 U.S.P.Q. 2d 1753 (Cal. S.C. 1990); see Noonan, W.D." Ownership of biological tissue." J.P.T.O.S., Vol. 72, 1990, pp.109-112; Churchill, J. "Patenting humanity: the development of property rights in the human body and the subsequent evolution of patentability of living things." I.P.J. Vol. 8, 1994, No. 249-284, pp. 273 and ff. For a similar discussion in Europe, see R. Moufang, 1993.

[l] Carty, B. "Genes for the taking." *Mediascan*, May 1, 1994, transcription of a CBC-Radio Network Report.

[m] *Amgen, Inc. c. Chugai Pharmaceutical Co.*, 706 F. Supp. 94 (D. Mass 1989); 13 *U.S.P.Q.* (2d) 1737 (D. Mass. 1990); et 927 F.2d 1200 (Fed. Cir. 1991); *Amgen, Inc. c. United States International Trade Commission*, 902 F.2d 1532 (Fed. Cir. 1990); *Genentech, Inc.* c. *The Wellcome Foundation Ltd.*, 14 *U.S.P.Q.* (2d) 1363 (Dist. Ct. Delaware 1990); *Genentech Inc's Patent*, (1989) *R.P.C.* 147 (C.A.) (United Kingdom); *Genentech Inc. v. Wellcome Foundation Ltd.*, 31 *U.S.P.Q.* 2d 1161 (CA FC 1994); *Hybritech, Inc. c. Monoclonal Antibodies Inc.*, 227 *U.S.P.Q.* 215 (Dist. Ct. of N.D. Cal. 1985); *Scripps Clinic & Research Foundation c. Genentech Inc.*, 666 F. Supp. 1379 (N.D. Cal. 1987); 707 F. Supp. 1547 (N.D. Cal. 1989); and 927 F.2d 1565 (Fed. Cir. 1991).

Eli Lilly independently developed its own HGH product Humantrope™, with a molecular structure that is *identical* to the HGH produced by the human body. Eli Lilly applied for orphan drug status and marketing approval for Humantrope, arguing that because of the additional amino acid on Protropin, the Eli Lilly was "different" from Protropin. In 1986 the FDA agreed, giving orphan status to Humantrope.

Genentech subsequently challenged the FDA's decisions in court by arguing the FDA did not have the authority to grant orphan status to Eli Lilly. The courts ruled against Genentech. Currently, each manufacturer has orphan status for its version of HGH, and each drug is sold on the market.

The results of the HGH case established that the FDA has the authority to determine when two therapies are sufficiently different from one another that each can receive its own orphan designation.[307]

Recombinant Erythropoietin - In June 1989, Amgen received approval to market its version of recombinant erythropoietin (rEPO) for the treatment of anemia in patients with chronic renal failure. EPO is a protein usually produced by the kidneys and necessary for the production of red blood cells. Amgen had first produced the drug in 1983 and had received orphan status for it in 1986. In September 1988, Chugai Pharmaceuticals of Japan, in a joint venture with Upjohn Pharmaceuticals, filed a product license application (PLA) with the FDA to market its own version of rEPO in competition with Amgen.

Although the Chugai/Upjohn drug has an amino acid structure identical to that found in the Amgen version, Chugai/Upjohn argued that the two drugs differed in glycosylation, the linkages of carbohydrates to the molecule, and that their version was therefore eligible for its own orphan designation and marketing approval. Although the FDA had not yet acted on the Chugai/Upjohn application for orphan drug designation at the time of the Amgen approval, then FDA commissioner Frank Young stated publicly that the Chugai/Upjohn version appeared "different" from the Amgen drug. In October 1989, Amgen requested that the FDA develop regulations to determine the circumstances under which two molecularly similar orphans are eligible for shared exclusivity.

The FDA recently attempted to set forth general criteria for determining when two drugs are sufficiently different to warrant orphan status and exclusivity for both. In proposed regulations published on January 29, 1991 (56 FR 3338) and adopted as final in December 1992, the FDA would presume two orphan drugs to be the same "if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior." According to these guidelines, different glycosylation patterns in two protein drugs, the difference suggested to have been found in the two versions of rEPO, would not be sufficient to find the Upjohn/Chugai drug different from the Amgen drug. The proposed regulations identify three circumstances under which a subsequent drug could be deemed "clinically superior" to an already approved orphan, and hence, approvable: (1) The subsequent drug is more effective than the first drug as shown in comparative clinical trials; (2) The subsequent drug is safer than the first for a "substantial portion of the target population", including the case where the two drugs have about the same therapeutic effect, the first drug has significant side effects, and the subsequent drug achieves its effect at a lower dose; or (3) The subsequent drug "makes a major contribution to health" as in the development of an oral dose form where the drug had only been available by parenteral administration.

While awaiting approval from the White House Office of Management and Budget to adopt a final version of the regulations, the FDA operated according to the draft regulations.[308]

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[307] Ibid

[308] Ibid

The clinical research tax credit, protocol assistance and clinical research grants theoretically lower the cost of orphan drug R&D in the United States. The market exclusivity provision increases the expected revenues to such R&D. In practice, the protocol assistance has had little effect, especially in recent years, and the tax credit and grants program represent, overall a relatively small commitment of U.S. federal funds to orphan products. This commitment may be critical for certain drugs, however, so it should not be discounted.[309] Concerns that the orphan drug law has subsidized the development of commercially successful drugs which did not really need help from the government led to legislation in the 102nd Congress that would have removed an orphan drug's exclusivity once cumulative net sales in the United States surpassed $200 million (S. 102-2060). Another piece of legislation (H.R. 102-1713) would tax "profits" on orphan drugs that exceed certain levels. Another measure of the law's effectiveness may be the extent to which orphan drugs have been sponsored by relatively small start-up firms. As drug R&D costs go up, smaller firms may have a harder time mustering enough resources to bring new products to market. By lowering barriers for such firms, the orphan drug subsidies may encourage competition in the industry and provide a new mechanism to realize the commercial benefits of biotechnological and other scientific discoveries, especially those originating in academia. Almost two thirds of orphan designations have gone to drug sponsors that are not PMA members, a characteristic commonly found among start-up firms.

Under the shelter of the U.S. orphan drug law, a number of U.S. biopharmaceuticals have emerged with commercial potential. There may be opportunities here for the consideration of Canadian IP policy makers.

6.4 Optimal IP Strategies for Canada

In this section, we respond to the request for advice on optimal strategies for IP protection to:

- encourage significant growth in Canadian biotechnology start-ups;
- attract sizeable foreign investments in R&D and manufacturing; and
- identify any constraints which may affect the pursuit of these objectives, while ensuring wide availability of new products and technologies at competitive prices.

In the context of an exhaustive examination of Canadian biotechnology, there simply hasn't been enough time to give proper examination to the varieties of recommendations for IP protection in biotechnology which would "optimize" value-added investments in Canada while ensuring competitive pricing and availability. We understand that the *Patent Act Amendments Act,* 1992, requires its provisions to be reviewed by the government in 1997. This review may lead to the reopening of the Act. In this section, we outline a framework

309 Ibid

for analyses and debate. In addition, we provide a number of recommendations (not necessarily complete) for evaluation for their economic benefits to Canada as part of a comprehensive analysis over the next two years. This activity should yield options for the Minister's consideration by 1997.

It is widely believed that, without the ability of health care biotechnology companies (in particular) to charge prices that will permit recovery of their investment both in a given biopharmaceutical as well as in failed attempts to find alternate drugs, the willingness to fund extensive research may be diminished.[310] To have the incentive to undertake R&D, a firm must be able to appropriate returns sufficient to make the investment worthwhile. The benefits consumers derive from an innovation, however, are increased if competitors can imitate and improve on the innovation to ensure its availability on favourable terms.

Patent law seeks to resolve this tension between incentives for innovation and widespread diffusion of benefits. A patent confers, in theory, perfect appropriability (i.e., monopoly of the invention) for a limited time in return for a public disclosure that ensures, again in theory, widespread diffusion of benefits when the patent expires.[311]

Previous investigations of the system suggest that patents do not always work in practice as they do in theory. On the one hand, appropriability is not perfect. Many patents can be circumvented; others provide little protection because of stringent legal requirements for proof that they are valid or that they are being infringed. On the other hand, public disclosure does not always ensure ultimate diffusion of an invention on competitive terms. For example, investments to establish the brand name of a patented product may outlive the patent itself. And patents may not always be necessary. Studies of the aircraft and semiconductor industries have shown that gaining lead time and exploiting learning curve advantages are the primary methods of appropriating returns. Other studies have emphasized the importance of complementary investments in marketing and customer service.[312]

In addition to these general considerations, the Canadian biotechnology industry has a number of unique defining features which shape its development.

- The Canadian market is too small by international standards to support the industry by itself. This immediately places Canadian NBFs at a competitive disadvantage with all foreign biotechnology firms with strong home markets, particularly U.S. firms.

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310 Kjeldgaard, R.H. and D. Marsh. "Health-Care Reform and Intellectual Property." *Bio/Technology*, Vol.12, June 1994, pp. 639-640

311 Levin, R.C., A.K. Klevorick et al. *Appropriating the returns from industrial research and development.* Brookings Papers on Economic Activity, Brookings Institute, Washington, DC, Vol. 3, 1987, pp. 783-831.

312 Ibid

- The size and global dominance of the American economy, the entrepreneurial aggressiveness of its culture and the incredible breadth and depth of support the U.S. government provides for biotechnological invention and commercial development all serve to nurture and support its indigenous biotechnology industry.

We hesitate to outline the competitive advantages American biotechnology enjoys for fear of underestimating their significance. Instead, we provide only a few comparative statistics on the relative commitments of our respective governments to biotechnology. The U.S. federal government has worked over the last three decades to enable the country to become the international leader in biotechnology research, development, and commercialization. To prevent any further erosion in its global leadership in this field, the Federal Co-ordinating Council for Science, Engineering and Technology (FCCSET) selected biotechnology research for special emphasis in the fiscal year 1994 federal budget. The goal of the U.S. Federal Biotechnology Research Initiative (BRI) is "to sustain and extend U.S. leadership in biotechnology research for the 21st century, in order to enhance the quality of life for all Americans, and to spur the growth of this important component of a healthy U.S. economy."[313] In 1993, 12 agencies participating in the BRI developed an integrated research strategy and identified four strategic objectives for the federal government's biotechnology research efforts.[314]

1. Extend the scientific and technical foundations for the future development of biotechnology.

2. Ensure the development of the human resource foundations for the future development of biotechnology.

3. Accelerate the transfer of biotechnology research discoveries to commercial applications.

4. Realize the benefits of biotechnology to the health and well-being of the population and the protection and restoration of the environment.

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313 *Biotechnology for the 21st Century: Realizing the Promise.* A Report by the Committee on Life Sciences and Health, A Supplement to the President's Fiscal Year 1994 Budget. Federal Co-ordinating Council for Science, Engineering and Technology, June 30, 1993

314 The following departments and agencies are participating in the U.S. federal government's Biotechnology Research Initiative: Agency for International Development, Department of Health and Human Services (the Centers for Disease Control and Prevention, the Food and Drug Adminsitration, and the National Institutes of Health), Department of Commerce (the National Institute for Standards and Technology and the National Oceanic and Atmospheric Administration), Department of Defense, Department of Energy, Department of the Interior, Department of Justice, Department of Veterans Affairs, Environment Protection Agency, National Aeronautics and Space Administration, National Science Foundation and Department of Agriculture.

- The 1994 BRI budget request was US$4.3 billion. By way of comparison, the Canadian government's 1991-1992 expenditures for biotechnology totalled an estimated $272.1 million (Table 4.7), or about 4.5 percent of the U.S. funding request (in converted currency). Comparisons, therefore, would dictate more than a twofold increase in Canadian government spending.

There are additional defining features. For around 25 years (1969 to 1993), Canada provided an IP environment conducive to the growth of Canadian generic drug and fine chemical industries. These industries have grown to the point where they could be the bedrock of a Canadian innovative pharmaceutical industry. With the changes wrought by Bill C-91 (including the regulatory amendments identified in Section 6.3), the generic drug industry contends that its revenue base is threatened, and that increased competition is causing outcomes not in Canada's economic interests. Others, however, have argued that Bill C-91 may provide some incentives that were not present with compulsory licensing for Canadian generic drug companies to become more innovative. Furthermore, this industry's revenue base has been supported significantly by the action of provincial drug formularies to reimburse only the least cost medications available (usually generic versions).

Part of Canada's uniqueness also arises from the fact that its generic drug industry and its health care NBFs face similar roadblocks to growth and development. Health care NBFs are cash strapped and are actively seeking strategic alliances with foreign multinationals to continue their commercialization activities. This sector faces the prospect of takeovers by foreign interests. In fact, it has already begun.

Are there legislative inducements within Canada's IP laws, policies and regulations which could tip the economic balance sufficiently to achieve several highly desirable economic, social and cultural goals? These goals could be defined as:

- to ensure continued competitive pricing for medicines in this country;
- to reduce Canada's growing pharmaceutical trade deficit;
- to improve access to capital for Canadian health care biotechnology firms' product development;
- to increase Canadian biotechnology R&D and manufacturing investments;
- to reduce Canada's growing trade deficit in the health care biotechnology sector; and
- to obtain (and retain) Canadian IP ownership of its biotechnology research.

Romer has provided one means of approaching these goals through the adaptation, to a Canadian context, of his proposal on industry investment boards.[315] Romer proposes an institutional arrangement that could provide more financial support for innovative activity and direct it toward areas with large economic payoffs. The aim is to create an independent source of funds for commercially relevant biotechnology research that would be under the

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[315] Romer, P.M. *Implementing a national technology strategy with self-organizing industry investment boards.* Brookings Papers: Microeconomics 2, 1993, pp. 345-399.

control of people in the biotechnology private sector who are knowledgeable about the opportunities. At the same time, Romer's concept could have a salutary effect on the threat to academic freedom posed by industry- sponsored biotechnology research. He notes that:

> an increased emphasis on practical problems is completely consistent with a division of labor in which universities concentrate on basic research, where free dissemination of knowledge is most important, and firms concentrate on R&D activities over which property rights should be strong. It would be very unwise for university researchers to perform proprietary research for private firms, yet many collaborations between business firms and universities or teaching hospitals are now taking precisely that direction. Universities in search of additional funding are increasingly seeking out arrangements under which they give up some of the traditions of open science and in effect become research subcontractors employed by private firms. Because the industry investment boards can solve, or at least mitigate, the free-rider problem, they can support universities and help set the research agenda without endangering the free exchange of ideas. Closer interaction between firms confronted with practical problems and researchers pursuing fundamental questions may lead not just to bigger economic benefits but also to better basic science.

At the risk of oversimplifying Romer's ideas, we outline briefly his economic rationale and then follow with his concept adapted to the goals identified above for the Canadian health care biotechnology sector.

Romer distinguishes between rival and non-rival economic goods. Rival goods (e.g., a car, a worker's labour, fish, clean air) are so named because consumers are rivals for their consumption. Once one person consumes the product, it is not available to others. However, individuals are not rivals for the consumption of non-rival goods, once produced. This category includes intellectual property such as biotechnology patents, trade secrets and designs. Romer notes several conclusions from contemporary economic research on endogenous growth. The first is that the production of non-rival goods makes growth possible. For instance, if the Earth returned to its physical state of 10,000 years ago, wiping out all structures, physical capital and civil engineering projects, but retaining the total stock of accumulated knowledge, he states that current standards of living would be recovered within a few generations. However, if the experiment were reversed, with the physical state of the world retained but the state of knowledge returned to its level of 10,000 years ago, our economic prospects would be much bleaker.

The second conclusion is that the usual invisible hand result (laissez-faire) applies only to an artificial economy in which non-rival goods are provided exogenously by nature. He notes:

> In a real economy, an inherent, unavoidable conflict exists between the incentives necessary to encourage the production of these (nonrival) goods and the incentives that lead to the optimal distribution of these goods, both to users and to the developers of other related nonrival goods. This means that private property rights and market exchange are not the perfect institutions for supporting growth. In fact, no simple description of the perfect institutional arrangement can exist. In any particular context, one must explicitly address the trade-offs both between the limitations of market mechanisms and those of political mechanisms.

Rival and non-rival goods can also be classified according to the strength of their property rights. With rival goods (or objects), land, for example, has relatively strong property rights because it is rarely stolen and the cost of maintaining its control is small compared to its market value. Automobiles have less strong property rights because they are more frequently stolen and society's total costs to maintain control are higher. Goods that are object-like (i.e., rival) over which near perfect control can be maintained are called private goods. A firm hiring a worker has weaker property rights and control over that person's labour services. Romer places commodities, such as fish in the sea, at the extreme end of this continuum for rival goods where little control is possible and property rights are virtually non-existent.

With non-rival goods, encrypted satellite television broadcasts are examples with very strong property rights. Further down in the continuum of strength of property rights are musical recordings, microprocessor design and computer code. Commercial firms are able to market these goods at significant mark up over marginal cost and earn a sizable rate of return. At the extreme end for non-rival goods are, for example, the results from research in physics whose use is virtually impossible to control. These are pure public goods, and not all public goods are provided by government (e.g., charitable donations).

If people have strong control over ordinary objects (i.e., private goods), and if there are many potential buyers and sellers, decentralized exchange between self-interested traders leads to efficient outcomes. This is the lesson of laissez-faire, or the invisible hand. If control over objects is weak, outcomes may be inefficient. In these situations, everyone is a free rider (protecting the environment falls into this category). While government action (e.g., by raising taxes to pay for the service) is one means of enhancing property rights for rival goods, it simply does not work for non-rival goods, where strong property rights are inherently associated with monopoly power. If there are strong property rights, there cannot be many sellers. If firms that produce non-rival goods are to avoid large losses, these goods must sell for a price that is higher than marginal cost.

Romer identifies two distinct problems in providing non-rival goods: how to share costs and how to select the most promising opportunities for investment. Real people will choose to be free riders if they can. They will not share the fixed costs of goods that are freely disseminated if they do not have to. Also, assembling all the information necessary to decide which of the extremely large number of possible non-rival goods to produce is very

difficult. The government's power of coercion makes it uniquely capable of solving the cost-sharing problem. However, governments have also wasted resources on non-optimal strategies. Markets can solve the sharing problem only by introducing monopoly distortions, but they are better than govemments at selecting the opportunities to pursue and at avoiding wasteful spending. Because people operating in the market are motivated by the potential for profit, they seek out only those non-rival goods that have real value. The parallel or simultaneous search by large numbers of market participants can efficiently evaluate many possibilities. Bankruptcy constraints quickly cut off the flow of resources to projects that turn out to be unpromising.

Under existing institutional arrangements for producing non-rival goods, one or the other of these extreme mechanisms is typically selected as being most appropriate for a given type of good. In the public good portion of the non-rival goods continuum, the government pays for basic research and gives away the result (Romer cites the example of the polio vaccine). At the other end of the continuum, society relies on market mechanisms to make investment decisions and accepts the limits on dissemination and the monopoly distortions that the use of the market entails.

The existing arrangement with government provision of basic research and market provision of final goods seems to work reasonably well for non-rival goods at the extreme ends of the continuum. It is the intermediate zone where the most important opportunities may be missed. This area may offer particularly large returns from investment in research. In our opinion, this is the area where the Canadian biotechnology community is situated. Romer's proposal mixes government and private sector mechanisms in such a way as to combine government's efficiency at solving free-rider problems with the market's effectiveness in selecting practical problems that offer the highest rates of return. Market participants can then make the right decisions about where the returns on investment are highest for the industry.

In adapting Romer's model, we suggest that the Minister of Industry could determine that collective action was necessary to address the Canadian health care biotechnology community's goals (as listed above) since independent action by individual firms would be ineffectual. This collective action could begin with a white paper identifying the industry-specific public good. The Minister could hold hearings to ensure that collective action did indeed address a genuine public need. The paper could specify a levy to be applied in the form of a tax on pharmaceutical sales. This tax initiative would be backed by the full force of law and imposed on the entire sector. The proceeds, however, would not go to the government. Instead, as Romer indicates, the plan would be to create an investment board that would fund a full range of worthwhile projects such as university-based research projects in biotechnology or the development of biotechnology manufacturing capability, and so on. For convenience, this proposed investment board is called the Canadian Health Care Biotechnology Development Board (CHCBDB).

In the absence of infinite price elasticity, taxation theory teaches that a tax on the producer of a good will be borne partly by the consumer. If the Canadian pharmaceutical market had a low price elasticity of demand, the proposed tax would be borne primarily by the

consumer. However, this market has for the last two decades been evolving in the direction of increased price competition as the direct result of the purchasing policies and practices of Canadian provincial formularies. Furthermore, private insurance plans are structured primarily on provincial formularies. It is, therefore, unclear how much of the tax would be borne by consumers. In any event, our recommendation incorporates a hearing process during which the views of the provinces, insurance companies and consumer groups could be considered.

The CHCBDB would have a board of directors drawn from the government and the Canadian biotechnology community and would operate as a quasi-private, non-profit foundation. The board would be limited by the terms of enabling legislation, as proposed in the white paper, but would otherwise have wide latitude to make decisions and would operate at arm's length from the political level of government. A general limitation would require the board to invest only in common property resources that benefit the entire community. For example, a specialized manufacturing capability (viz., fermentation machinery) would be made available (for sale or lease) to all Canadian health care biotechnology firms on equal terms. Funded university research would be owned by the resident university (following the model of the Harvard sample described above) but could be licensed to all Canadian health care biotechnology firms on equal terms.

Romer notes that the enabling legislation should also specify that absolutely no board funds could be used to support lobbying, public relations or any kind of political activity. Nor would direct or indirect kickbacks or side payments to firms in the industry be permitted. He suggests a tax rate of less than 2 percent. At 1 percent to 2 percent of pharmaceutical sales, this would amount to some $100 million to $200 million of funding per year (depending on whether prescription and over-the-counter medicines are both included). He also notes that the legislation should articulate the general principle that the tax is a domestic consumption tax rather than a production tax. Units produced domestically for sale abroad would not be subject to the tax, but units produced abroad and sold domestically would. The legislation would also mandate equal treatment for all members of the community.

With this rationale in mind, we make the following recommendation.

> ***Recommendation 1:*** *That the Minister of Industry introduce a white paper to address the public good as identified in the Canadian health care biotechnology community's goals (listed above). The Minister could hold hearings to ensure that the collective action called for in the white paper did indeed address a genuine public need. The paper could propose a levy in the form of a tax on domestic pharmaceutical sales. This tax initiative would be backed by the full force of law and imposed on the entire sector. The proceeds, however, would not go to the government but would, instead, be used to create an investment board [called the "Canadian Health Care Biotechnology Development Board" (CHCBDB)] that would fund a full range of worthwhile health care biotechnology projects, including university-based research and the development of biotechnology*

manufacturing capability.

The CHCBDB would have a board of directors drawn both from the government and the Canadian biotechnology community and would operate as a quasi-private, non-profit foundation. The board would be limited by the terms of the enabling legislation but would otherwise have wide latitude to make decisions and would operate at arm's length from the political level of government. A general limitation would require the board to invest only in common property resources that benefit the entire industry.

The enabling legislation should also specify that absolutely no board funds could be used to support lobbying, public relations or any kind of political activity. Nor would direct or indirect kickbacks or side payments to firms in the industry be permitted. A suggested tax rate of 1 percent to 2 percent of pharmaceutical sales would generate some $100 million to $200 million in funding per year (depending on whether prescription and over-the-counter medicines are included). The legislation should articulate the general principle that the tax is a domestic consumption tax rather than a production tax. Units produced domestically for sale abroad would not be subject to the tax, but units produced abroad and sold domestically would. The legislation would also mandate equal treatment for all members of the Canadian biotechnology community.

Earlier, we reported a number of current IP issues identified during our discussions with members of the Canadian biotechnology community. Prominent among them is the section 55.2 issue which has apparently introduced inequities and inefficiencies into the Canadian pharmaceutical market and increased costs to Canadian consumers of medications. By erecting a barrier to competition on patent expiration, the regulation appears to contradict the intent of the new patent regime established under Bill C-91 amendments to the *Patent Act*. In this respect, the PMPRB has stated that "Bill C-91...established a new regime to facilitate the entry of competitors immediately upon the expiry of a patent, to stockpile and seek regulatory approval of products prior to the expiry of a patent.... These amendments appear to have been designed to ensure patentees enjoy the benefits of their statutory rights during the normal patent term, but not beyond it."[316] As a result, we make the following recommendation.

Recommendation 2: *That the section 55.2 amendment to the Regulations of the* Patent Act *(resulting from Bill C-91) be abolished as quickly as possible, and that the Minister of Health's* de facto *injunction be lifted from all relevant cases now before Canadian courts to allow the corresponding applications for regulatory approval for generic drug products to proceed*

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316 Patented Medicine Prices Review Board, "Dedicated Patent - Notice and Comments." *PMPRB Bulletin*, Issue No. 15, January 1995, pp. 5-8.

expeditiously to the issuance of their notice of compliance.

We raised the issues of broad blocking patents and their dampening effect on innovation and the development of the Canadian biotechnology industry. We also discussed the difficulties associated with a policy allowing a deferral of up to seven years for the examination of a patent application. Abolishing this deferral would intensify the demand for resources at CIPO for patent examination. In some instances, patentees abandon their patents before examination with a saving to CIPO in resource use. There are trade-offs as a result, and our recommendation below reflects this fact. We also noted that the EPO has provided one very effective remedy to patent applicants to challenge the existence of such patents and to raise other objections concerning the implications of patent applications. As a consequence, we make the following two recommendations.

> ***Recommendation 3:*** *Since broad blocking patents impede the development of Canadian new biotechnology firms, the Canadian Intellectual Property Office should avoid issuing broad blocking patents by determining the subject matter of the invention and should grant claims that cover that subject matter only. This involves assessing whether the subject matter of the invention is really a product (where claims to the product will create barriers to the development of the industry) or a process of manufacturing or use of a product (where claims to the process will provide patent protection but not impede the development of the industry).*
>
> *The period of deferral for examination of patent applications should be reduced from seven years to five years.*
>
> *The Canadian Intellectual Property Office should create written and published policies on the breadth of claims for biotechnology inventions.*

> ***Recommendation 4:*** *That the Minister consider amendments to the* Patent Act *providing for an opposition appeal process at the Canadian Intellectual Property Office similar to that available at the European Patent Office. The process should allow challenges to applications for broad blocking patents within a review period (e.g., nine months) and at small cost to the challenger.*

We provided a cursory review of some of the advantages accruing to U.S. NBFs seeking to commercialize their biotechnology products under the provisions of the U.S. orphan drug law. The following recommendation seeks to level the playing field on this matter for Canadian NBFs.

> ***Recommendation 5:*** *That the ministers of Industry, Health and other relevant departments should consider passage of a law similar in scope to the U.S. orphan drug law to provide Health Protection Branch assistance to Canadian new biotechnology firm orphan drug developers in protocol design for new drug approval or product licence approval applications, research grants for clinical and preclinical studies of orphan products, specific R&D tax credits and a grant of a period of market exclusivity to the first Canadian new biotechnology firm that receives approval for an orphan drug.*

Interviewees emphasized the critical importance of a proactive federal government monitoring and negotiating role to mitigate the effects of proposed and enacted legislation of foreign countries on Canadian NBFs. Examples provided during interviews included the U.S orphan drug law (for which a separate recommendation is provided above) as well as the U.S. Boucher Bill and the U.S. reduction to practice legislation. Where proposed or enacted legislation harms Canadian NBFs, the federal government should work with these countries to try to reduce the adverse impact of their legislation. Or it should consider adopting similar practices in Canada. Accordingly, we make the following recommendation.

> ***Recommendation 6:*** *That the Minister of Industry consider the establishment of a biotechnology advisory body to monitor and advise on the effects of proposed and enacted policies, practices and legislation of foreign countries on Canadian new biotechnology firms. A high priority activity of this body should be to undertake an analysis of protectionist measures and preferential treatment afforded foreign biotechnology companies by their home governments through intellectual property provisions and/or regulatory and other agencies. Where proposed or enacted policies, practices or legislation harm Canadian new biotechnology firms, the federal government should work with these countries to try to reduce their adverse impacts. Failing this, the federal government should consider the adoption of similar Canadian policies, practices and legislation.*

We noted that article 4*bis* of the Paris Convention of 1883 allows for a complete patent term in any particular country of the Union (e.g., Canada) based on the date of filing of the application in that country, despite the apparent inequity set up by the fact that this date might follow the priority date for the patent in some other country of the Union (viz., the United States) by up to one year. However, we argue on the grounds of economic benefit that there should be no prohibition to manufacture in Canada for export purposes during the time when a patent has expired in another country (e.g., the United States) but is still valid in Canada. By locking out Canadian generic drug companies from this export market, e.g., the U.S. market, during this critical period, U.S.-based multinationals obtain a competitive advantage which they use to control the generic market for a given pharmaceutical with an expired patent. And with the rise of managed care organizations in the United States, the

generic business in that country is growing rapidly. Canadian patent law appears, therefore, to set up a non-tariff trade barrier which works to the disadvantage of Canadian industry. To remove this impediment, we provide the following recommendation.

> ***Recommendation 7:*** *That the Minister of Industry or appropriate counterpart consider amendments allowing the manufacture, for export, of pharmaceutical products still under an existing patent in Canada to countries where the corresponding patents have expired.*

We noted that NAFTA (paragraph 12 of article 1709) recognizes the appropriateness, in certain instances, of extending a patent term. Although NAFTA recognizes patent term extension, it is not currently available in Canada under the *Patent Act*. Patent term restoration has been implemented in the United States, Europe and Japan. In view of the increased regulation proposed for biotechnology products and processes, Canadian biotechnology firms would benefit from a change to Canada's laws to provide for patent term restoration. Accordingly, we make the following recommendation.

> ***Recommendation 8:*** *That the Minister of Industry consider amendments to the* Patent Act *to provide for the extension of a patent term in certain appropriate instances (viz., following prolonged regulatory review).*

GLOSSARY OF TERMS AND ABBREVIATIONS

Aerated pile method - Method of composting for the decomposition of organic waste material where the wastes are heaped in separate piles and forced aeration provides oxygen.

Anaerobic - The absence of oxygen; able to live or grow in the absence of free oxygen.

Anaerobic digester - A secondary sewage treatment facility used for the degradation of sludge and solid waste.

Bioaccumulation - Accumulation of polutant residues in the environment.

Bioavailability - The degree of availability of pollutants in contaminated soil or land to biodegradation.

Biocatalyst - An enzyme, used to catalyze a chemical reaction.

Biodegradable - A substance that can be broken down into smaller molecules by the action of biological systems.

Biodegradation - The microbially mediated process of chemical breakdown of a substance to smaller products caused by microorganisms or their enzymes.

Biodiversity - The variety of different types or species of organisms occurring together in a biological community.

Biofilm - A microbial community occurring on a surface as a microlayer.

Biofilter - A device used for the bioremediation of polluted air consisting of an immobilized microbial community as a biofilm through which the air is passed to detoxify contaminants.

Biogas - Gas produced by anaerobic microorganisms, primarily methane (in concentrations of 60 percent to 70 percent, the remainder being CO_2).

Biomass - All organic matter that derives from the photosynthetic conversion of solar energy; the total mass of living organisms in an ecosystem.

Biopharmaceutical - Pharmaceutical product (either a diagnostic, therapeutic or vaccine product) manufactured using biotechnology.

Biopolymer - Naturally occurring macromolecules including proteins, polysaccharides and nucleic acids.

Bioreactor - A contained vessel or other structure in which chemical reactions are carried out (usually on an industrial scale), mediated by a biological system, enzymes or cells.

Bioreclamation - Use of biological systems to reclaim valuable products from waste streams.

Bioremediation - The use of biological agents to reclaim soils and waters polluted by substances hazardous to human health and/or the environment. It is an extension of biological treatment processes that have traditionally been used to treat wastes in which microorganisms typically are used to biodegrade environmental pollutants.

Biosensor - An immunological or genetic technique for detecting chemicals or microbial activity, based on the generation of light and/or an electrical signal.

Biotechnology - The application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms.

Biotechnology firm - An individual, corporation or business which researches, develops or commercializes biotechnological inventions.

BOD - Biological or biochemical oxygen demand. The amount of oxygen required to oxidize completely the organic matter in a water sample.

Broad blocking patents - Patents having broad claims which may prevent other persons from manufacturing, using or selling biotechnologicy products or from using a process to manufacture biotechnology products.

Broad blocking patent applications - Patent applications having broad claims which, on issuance, may prevent other persons from manufacturing, using or selling biotechnology products or from using a process to manufacture biotechnology products.

CDMA - Canadian Drug Manufacturers' Association, which represents Canadian generic drug manufacturers and several Canadian active ingredient manufacturers and industry suppliers.

CEPA - *Canadian Environmental Protection Act.*

CIPO - The Canadian Intellectual Property Office, which includes examiners of patent applications for biotechnology products or processes, the Patent Appeal Board and the Commissioner of Patents of the Canadian Patent Office, Industry Canada.

COD - Chemical oxygen demand. See BOD above.

Compulsory licensing - A licence granted by the Commissioner of Patents that permits the licensee to import, make, use or sell a patented invention pertaining to a medicine. The compulsory licensee pays licence fees or royalties to the patent holder for use of the patented invention. The 1993 amendments to the *Patent Act* eliminated compulsory licensing effective December 21, 1991.

Consortium - An interactive association between microorganisms that generally results in combined metabolic activities.

DNA - Deoxyribonucleic acid, a polymer composed of deoxyribonucleotide units; genetic material of all organisms except RNA viruses.

DSL - The Domestic Substances List under the *Canadian Environmental Protection Act* (CEPA) contains all substances known to have been manufactured, imported or in commerce during the three- year period (1984 to 1986), and is the basis for determining whether a substance is new to Canada. Substances specified on the DSL are not considered new to Canada and will not require notification under the NSNRs. See Section 5.1 for a fuller definition.

Enrichment culture - Any form of culture in a liquid medium that results in an increase in a given type of organism while minimizing the growth of any other organism present.

Enzyme - A protein which catalyzes the conversion of a substrate to a product.

EPA - The U.S. Environmental Protection Agency, the environmental regulator in the United States. The Canadian responsibility is held by the federal department, Environment Canada.

ELISA - Enzyme-linked immunosorbent assay - A technique used for detecting and quantifying specific serum antibodies based on tagging the antigen-antibody complex with a substrate that can be enzymatically converted to a readily quantifiable product by a specific enzyme.

Ex-situ - Off site, usually used in soil remediation to include treatment in which soil is removed to another location for treatment.

FDA - the Food and Drug Administration, an agency of the U.S. government responsible for the regulation of food and drugs sold in that country. Its counterpart in Canada is the Health Protection Branch (HPB).

FIPCO - Fully Integrated Pharmaceutical Company, a traditional model for pharmaceutical and biotechnology firms characterized by vertical integration, hierarchical organization and with the infrastructure to eliminate or reduce the need for contracting out development and marketing activities.

Floc - A mass of microorganisms cemented together in a slime produced by certain bacteria, usually found in waste treatment plants.

Flocculant - An agent that causes small particles to aggregate (flocculate).

FTE - Full-Time Equivalent Employees. It is equal to the sum of full-time employees and part-time employees (expressed as fractions of full-time employees).

GATT - the General Agreement on Tariffs and Trade.

GEMs - Genetically engineered or modified microorganisms.

Generic biotechnology firm - A Canadian biotechnology firm which manufactures, uses or sells patented biotechnology products under a compulsory licence; and includes a firm which manufactures, uses or sells a patented medicine once its patent expires.

Genetic engineering - The deliberate modification of the genetic properties of an organism by the application of recombinant DNA technology.

Genome - The genetic endowment of an organism. All genetic information within an organism. When expressed, it results in the observable characteristics or phenotype.

Groundwater - Sub-surface water in a terrestrial environment.

HPB - Health Protection Branch, located in the federal department Health Canada, is the government's regulator of the safety and efficacy of food stuffs, medicines and medical equipment sold in this country.

Hybridoma - Hybrid cells produced through the fusion of two types of cells, antibody-producing B lymphocytes and quasi-immortal cancer cells from mice. The resulting hybridomas secrete large amounts of homogeneous antibodies. The hybridomas have the ability to grow indefinitely in cell culture and can produce an almost unlimited supply of a specific "monoclonal" antibody. By immunizing mice with specific antigens (or foreign substances), researchers can create and select hybridomas that produce a culture of specific, desired monoclonal antibodies.

Immobilization - The binding of organisms, cells or enzymes to a substrate such as activated carbon in order to permit the easier separation of reaction products.

Immunoassay - An analytical method that makes use of an antibody which interacts specifically with an antigen (analyte), allowing the quantification of the target analyte.

Innovative biotechnology firm - A Canadian biotechnology firm which owns a patent for a medicine.

In-situ - On site, usually used in soil remediation to mean treatment without moving (digging out) the soil.

Intermediate-sized biotechnology firm - A firm which manufactures, uses, sells or performs R&D on biotechnology products, and employs 26 to 100 persons.

Invention - Has the meaning set out in Canada's *Patent Act* and means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter.

IP - Intellectual property including patents, trade secrets, plant breeders' rights, industrial designs, copyright, trademarks and other forms of intellectual property.

IPO - Initial Public Offering of a company seeking to enter public markets for the purpose of raising investment capital and becoming a publicly traded and listed firm.

IPPD - Intellectual Property Policy Directorate, Industry Canada.

IRAP - Industrial Research Assistance Program of the National Research Council which funds technology transfer (TT) positions in Canadian universites.

Landfill - A site where solid waste is dumped and allowed to decompose; a process in which solid waste containing both inorganic and organic material is deposited and covered with soil.

Large-sized biotechnology firm - A firm which manufactures, uses, sells or performs R&D on biotechnology products, and employs more than 100 persons.

Leachate - The liquid product of leaching.

Leaching - The removal of a soluble compound, such as an ore, (also soluble organic compounds) from a solid mixture by washing or percolating.

Licensed biotechnology firm - A Canadian biotechnology firm which has a licence to manufacture, use or sell a patented product or process including a patented medicine.

Member of the Canadian biotechnology industry - An officer or employee of a Canadian biotechnology firm who obtains and maintains IP protection for biotechnology inventions. With the exception of the quotations provided in this report, all of which appear in published articles, interviewed persons have provided their views on the condition of anonymity.

MRC - Medical Research Council of Canada

Microbe - Microorganism.

Microbial ecology - The field of study that examines the interactions of microorganisms with their biotic and abiotic surroundings.

Microorganisms - Microscopic organisms, including algae, bacteria, yeasts, fungi, protozoa and viruses.

MAbs - Monoclonal Antibodies.

Mutual organization - is another organizational model for biotechnology firms in which the parties are both principals and agents, and learning to work together presumably also prevails in this co-contracting mode. The major difference from quasi-firm lies in risk allocation. There is asset specificity in the transaction in the forms of learning to work together and the investment of tangible and intangible assets by all parties. The mutual organization differs from a fully integrated firm because of communication and co-ordination problems between principals and members who will try to appropriate the results for their own profit and because the participating firms only transfer a portion of their assets to the organization.

NAFTA - North American Free Trade Agreement.

NBF - New Biotechnology Firm.

NBS - National Biotechnology Strategy organized by the federal government in 1983 and administered under two committees, the National Biotechnology Advisory Committee (NBAC) and the Interdepartmental Committee on Biotechnology (ICB).

NOMs - Naturally occurring microorganisms.

NSERC - Natural Sciences and Engineering Research Council.

NSNRs - New Substances Notification Regulations under CEPA.

Patent - A monopoly limited in time and granted by the state for a new invention. A patent gives the patentee the exclusive right to make, sell or otherwise exploit the invention.

PCR - Polymerase chain reaction, a technique using the enzyme polymerase to produce many copies of a nucleotide sequence.

Pesticide - Chemical product used to destroy pests (e.g., insecticide, herbicide).

pH - The symbol used to express the hydrogen ion concentration in a solution, and signifying the logarithm to the base 10 of the reciprocal of the hydrogen ion concentration. A neutral solution has a pH of 7; increasing acidity implies lower pH values, while increasing base solutions have higher pH numbers.

Phenotype - The characteristics of an organism that result from the interaction of its genetic constitution with the environment.

Photosynthesis - The synthesis by plants of organic compounds from carbon dioxide and water using light energy absorbed by chlorophyl.

Pioneer - Product or process that is a major invention and does not simply improve an existing product or process.

PMAC - Pharmaceutical Manufacturers' Association of Canada, the Canadian equivalent to the Pharmaceutical Manufacturers' Association (PMA) in the United States.

PMPRB - The Patented Medicine Prices Review Board created by the *Patent Act*, as amended. The Board reviews the prices of patented medicines in Canada, determines whether the pricing of such medicines is excessive and imposes penalties when manufacturers excessively price patented medicines or engage in a policy of excessive pricing of patented medicines.

Practitioner - A lawyer or agent who works with Canadian and multinational biotechnology firms or within a Canadian biotechnology firm to obtain and maintain IP protection for biotechnology inventions. Most Canadian IP practitioners represent multinational biotechnology firms. With the exception of the quotations provided in this report, all of which appear in published articles, interviewed persons have provided their views on the condition of anonymity.

Quasi-firm - An intermediate organizational model for biotechnology firms using a co-ordinated contracting mode which relates a prime contractor as principal and a group of sub-contractors as agents in a long-term, risk-sharing relationship.

R&D - Research and Development, a term encompassing all basic and applied research as well as product developmental activities and associated costs.

rDNA - Recombinant DNA, a DNA molecule formed by joining DNA segments from two or more sources.

SA - Scientific Authority of officials from three federal departments (Environment Canada, Health Canada and Industry Canada) overseeing this project.

Scope of IP protection - The subject matter and breadth of claims awarded by a Patent Office to an applicant seeking a patent for a biotechnology invention including whether the Patent Office awards claims to plants or animals, or to methods of medical treatment, or to isolated and purified naturally occurring products; requires that claims be restricted to products prepared by their process of manufacture; and awards broader claims to "pioneer" inventions than to inventions which improve on existing products or processes.

Small-sized biotechnology firm - A firm which manufactures, uses, sells or performs R&D on biotechnology products, and employs 11 to 25 persons.

Substrate - The chemical substance acted on by an enzyme; a base support on which other material is deposited, adsorbed or immobilized.

Terms of reference - The terms of reference for the Background Economic Study on the Canadian Biotechnology Industry (1993-1994) performed on behalf of three federal departments (Environment Canada, Health Canada and Industry Canada).

TRIPs - Trade Related aspects of Intellectual Property Treaty.

TSCA - the U.S. *Toxic Substances Control Act.*

UPOV - International Convention for the Protection of New Varieties of Plants. Enacted in 1961.

USPTO - United States Patent and Trade Mark Office.

UST - Underground Storage Tanks, the removal management of which is a major market activity for environmental bioremediation in Canada, the United States and Europe.

Very small biotechnology firm - A firm which manufactures, uses, sells or performs R&D on biotechnology products, and employs one to 10 persons.

VIPCO - Virtually Integrated Pharmaceutical Company, a new model for biotechnology firms which contract out much of their developmental and marketing activities.

Virus - A non-cellular entity that consists minimally of protein and nucleic acid and that can replicate only after entry into specific types of living cells, and then only by making use of the cell's own systems.

WCS - World Competitiveness Scorecard, a construct designed by a Swiss-based consortium using a blend of quantitative methods and judgment to measure the international competitiveness of industrialized and newly emerging economies. A total of 381 criteria are used, two thirds of which come from national statistics and the other one third from an opinion survey of 16,500 business executives around the world.

Yeast - A category of fungi defined in terms of morphological and physiological criteria; typically unicellular, saprophytic organisms that characteristically ferment a range of carbohydrates; commercially used for brewing, wine making and bread making.