SECTOR COMPETITIVENESS FRAMEWORKS

BIO-INDUSTRIES

PART 1 – OVERVIEW AND PROSPECTS

Industry Sector
Bio-Industries

Secteur de l'industrie
Bio-industries

Canada

BIO-INDUSTRIES

PART 1 – OVERVIEW AND PROSPECTS

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This *Overview and Prospects* is the first of two companion documents on Canadian bio-industries in the **Sector Competitiveness Frameworks** series, which is being produced by Industry Canada in collaboration with Canada's key stakeholders in the industry. *Part 2 — Framework for Action* will be prepared in coming months, based on discussions with major industry stakeholders, following study and review of the *Overview and Prospects*.

The **Sector Competitiveness Frameworks** series focusses on opportunities, both domestic and international, as well as on challenges facing each sector. The objective is to seek ways in which government and private industry together can strengthen Canada's competitiveness and, in doing so, generate jobs and growth.

Part 1 — Overview and Prospects is being made available for distribution in printed as well as electronic forms. In all, some 31 industrial sectors are being analyzed.

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FOREWORD

The new Canadian marketplace is expanding from national to global horizons and its economic base is shifting increasingly from resources to knowledge. These trends are causing Canadian industries to readjust their business approaches, and government must respond with new tools to help them adapt and innovate. Industry Canada is moving forward with strategic information products and services in support of this industry reorientation. The goal is to aid the private sector in what it is best qualified to do — create jobs and growth.

Sector Competitiveness Frameworks are a series of studies published by Industry Canada to provide more focussed, timely and relevant expertise about businesses and industries. They identify sectors or subsectors having potential for increased exports and other opportunities leading to jobs and growth. They cover 31 of Canada's key manufacturing and service sectors.

While they deal with "nuts and bolts" issues affecting individual sectors, the Sector Competitiveness Frameworks also provide comprehensive analyses of policy issues cutting across all sectors. These issues include investment and financing, trade and export strategies, technological innovation and adaption, human resources, the environment and sustainable development. A thorough understanding of how to capitalize on these issues is essential for a dynamic, job-creating economy.

Both government and the private sector must develop and perfect the ability to address competitive challenges and respond to opportunities. The Sector Competitiveness Frameworks illustrate how government and industry can commit to mutually beneficial goals and actions.

The Sector Competitiveness Frameworks are being published sequentially in two parts. An initial *Overview and Prospects* document profiles each sector in turn, examining trends and prospects. The follow-up *Framework for Action* draws upon consultations and input arising from industry–government collaboration, and identifies immediate to medium-term steps that both can take to improve sectoral competitiveness.

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1 HIGHLIGHTS

The objective of this examination is to review the key characteristics and prospects for Canadian bio-industries in order to determine the factors affecting competitiveness and the ability of biotechnology to generate jobs and growth for Canadians.

1.1 Distinguishing Characteristics

Biotechnology, broadly defined, is the applied use of living organisms or their components to make or modify products, to improve plants or animals and to develop micro-organisms for specific uses. This definition encompasses both the new biological tools of genetic engineering, cell fusion and protein engineering as well as the traditional techniques of fermentation used in wine and beer production and classical breeding for selecting improved plants and livestock. ***A narrower definition (often called "new" or second-generation biotechnology) restricts the term to the use of recombinant DNA, monoclonal antibody and other modern techniques arising from applications of molecular biology.*** For purposes of analysis, the report will focus on the latter meaning unless otherwise noted.

Biotechnology is not so much a separate industry as a set of tools with applications across a wide range of industries, from health care to agri-food, environment and the resource sectors, serving as a catalyst to sustainable development. It can lead to new, improved and less expensive products and processes such as the discovery of new drugs and earlier detection and control of diseases; help reduce pollution; and provide crops and food with better yields, value-added traits and processing qualities. However, biotechnology also gives rise to a number of concerns. These include fears about the long-term survival of micro-organisms once they have been released and fears they will proliferate in unexpected ways or in an uncontrolled manner. Considerable controversy exists worldwide concerning the extension of patents to genetic material and life forms and the labelling of food derived from biotechnology.

There are wide differences in the rate at which biotechnology is being adopted. Human health is the most commercially successful application, accounting for over 90 percent of biotechnology products on the market. Biotechnology in agri-food (shortened to ag-bio-tech) is a major source of innovation, but its acceptance in the marketplace is still being debated. Meanwhile in other industries such as mining, forestry and pulp and paper, applications are still in the formative stage. Product development largely depends on the resources and strategies of individual companies as well as technical and market forces peculiar to each sector. Governments can create a policy environment that is conducive to the adoption of biotechnology in key sectors of the economy.

Dedicated biotechnology companies — firms created specifically to exploit the commercial potential of biotechnology — are concentrated in the United States, the United Kingdom, France, Canada and Germany. These countries have strong research infrastructure, capital and the industrial capacity to convert basic research into products. The United States, with its particularly strong research base in health care and agriculture, dominates the global market. Canada is several years behind the U.S. in commercialization.

Canada's biotechnology industry has strengths in certain niche areas such as vaccines. Moreover, its medical research infrastructure has initiatives in therapies for cancer, acquired immune deficiency syndrome (AIDS) and neurodegenerative diseases. The University of Toronto and its affiliated teaching hospitals comprise the largest medical faculty in North America. A related Canadian strength on the services side is in providing clinical trial services to test the safety and effectiveness of new drugs. These organizations have developed a solid reputation in the U.S. and Europe in large part due to the experience of their medical staff in conducting clinical trials, Canada's large, multi-ethnic patient base, and a public health care system that provides comprehensive patient information and tracking.

In the area of crops and animals, Canada has strong research clusters at the universities of Guelph and Saskatoon as well as at the National Research Council's Plant

Biotechnology Institute in Saskatoon and at its Institute for Marine Biosciences in Halifax. Competitive strengths lie in animal husbandry (embryo transplants and high-quality bovine semen), plant breeding of genetically engineered canola and potatoes, aquaculture vaccines and brood stock optimization, yeast strains and bacterial cultures, and somatic embryogenesis for propagation of conifers and flowers.

1.2 Major Trends

The greatest impact of biotechnology worldwide has been in human health care. This is expected to continue due to consumer demand for innovative, life-saving drugs, high levels of government funding for basic biomedical research, and the greater availability of investment capital than in other fields because of the prospect of higher returns. In other sectors, margins are much lower and biotechnology is often not a replacement for established tools but an additional approach to solving problems. Consumer acceptance is particularly critical in agri-food if biotechnology is to make significant inroads in the market.

Many of the leading dedicated ag-bio-tech firms in North America have ceded ownership to large multinational chemical and agricultural corporations. This trend toward acquisition and consolidation coupled with relatively low returns on ag-bio-tech stocks hold little promise for strong growth for agri-food biotechnology startups.

Throughout the world, government financial and policy support has been critical. Such support is needed for basic research, financial assistance to fledgling firms, intellectual property protection, and regulations that expedite commercialization and build consumer confidence in products. The health care industry in particular has been proficient in using government-funded basic research in universities and teaching hospitals for commercial development.

The international regulatory environment is a major factor in international competitiveness. It affects market access, ability to raise capital,

costs and investment decisions. In response to Canadian industry need for an efficient, predictable and flexible regulatory system, products of biotechnology will continue to be administered by existing legislation and regulatory agencies.

Financing is critical. Worldwide, the biotechnology industry, and the health care sector in particular, has experienced losses since inception because of heavy investments in research and development (R&D) and long lead times to commercialization. Bringing a new diagnostic product to market takes three to five years and between $1 million and $20 million; for a new crop variety or a new drug, the time is eight to 12 years and the cost is between $150 million and $250 million. The biggest challenge facing companies in ag-bio-tech is to secure a reasonable return, as prices or margins for many products will not necessarily be higher than traditional products.

Because biotechnology is research-intensive and employs many people who are highly skilled in a variety of areas, Canada's generous R&D tax credits are extremely important to emerging Canadian companies. These incentives also support a strong academic base and enhance employment opportunities for scientists and technicians.

As Canadian firms advance toward commercialization, the human resources needs will shift. Staff requirements differ at each stage in a product or service life cycle, from early-stage research, toward product and process development, to scale-up, formulation and clinical trial design and on to regulatory affairs. Managers with expertise in public stock offerings, investor relations and international business development will also be required. The changing nature of biotechnology research will also require a number of highly specialized scientists with skills in peptide chemistry, gene therapy and bioinformatics, for example. Shortages of qualified personnel are starting to appear. Firms are increasingly being forced to look outside the country for people with specific expertise in bioprocessing and preparation of regulatory submissions; the Canadian industry does not yet have the manufacturing expertise to nurture these skills in-house.

In terms of geographic markets, the United States will remain the first market of choice and the major source of investment. A major challenge for aspiring entrants into the U.S. market is meeting the stringent requirements for health care products set by the U.S. Food and Drug Administration.

The worldwide market for biotechnology-based products is expected to grow from US$15 billion in 1995 to US$38 billion in 2005. Biopharmaceuticals will continue to hold the dominant share, but growth is expected to slow to 3 percent a year over the rest of the decade, as fewer blockbuster drugs are on the immediate horizon. Immunodiagnostics are the next largest application for biotechnology, with sales projected to increase 9 percent a year. However, this is a difficult subsector in which to succeed, because international markets are facing pressures to control or lower health care costs and the markets are already dominated by multinational firms. The strongest growth is projected for the agri-food sector, particularly transgenic plants and animal health care. In aquaculture biotechnology, opportunities include fish vaccines and pool-side diagnostic tests as well as genetic improvement programs to optimize fish growth rates and feed conversion efficiency. However, compared with other sectors, the application of aquaculture biotechnology is in its infancy because of incomplete scientific knowledge about marine organisms and fish pathogens and genetics. The present small market size along with a costly and burdensome regulatory process has also made it difficult to finance extensive R&D and commercial development.

1.3 The Bottom Line

Modern biotechnology has the potential to make a significant contribution to the Canadian economy and to sustainable development through its impact on key sectors such as health care and agri-food.

Although Canada is not yet a major commercial competitor, it has made important contributions to R&D and has many promising startup and development stage companies with potential in selected niches. There are significant global opportunities but, despite the strong academic research base and magnitude of public and private investment,

commercialization has been slow. As in other countries, it has not developed at the pace predicted by early, often optimistic, forecasts.

The major challenges for governments and industry include:

- addressing consumer concerns with respect to health, safety, information, ethics and the environment, and balancing these against the costs of regulation
- maintaining a strong academic research base and fostering technology transfer mechanisms and industrial capability to convert research into products
- building a domestic manufacturing capability by ensuring competitive costs and returns (i.e. quantifying relative production costs and making the case for investment)
- improving the diffusion of the technology to other sectors of the economy and determining what factors influence its adoption
- improving coordination of training and strategic planning of human resources requirements
- addressing the financing issues — particularly for early-stage, non-health care companies
- attracting investment and alliance partners to support the cost of clinical trials, regulatory approval and international marketing.

2 KEY POINTS ABOUT THIS INDUSTRY

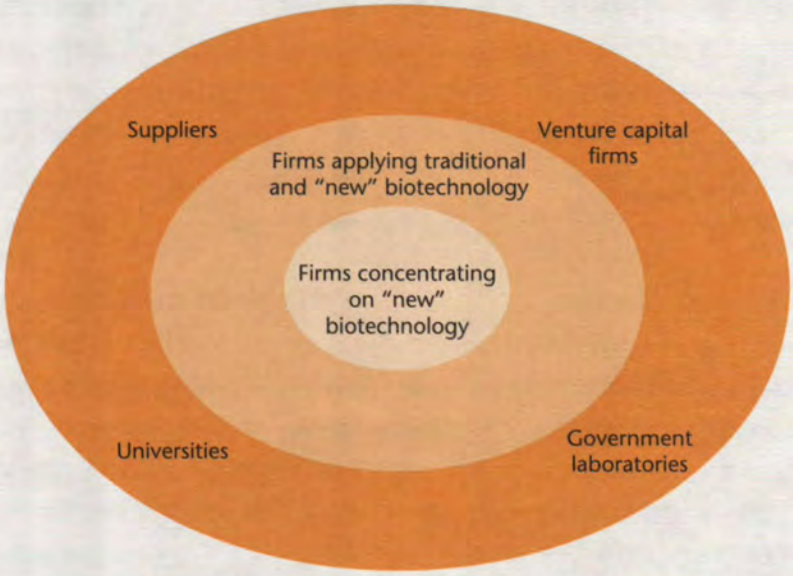
Many diverse sectors make up bio-industries . . .

Biotechnology is an umbrella term that covers a wide spectrum of scientific tools based on molecular biology. Formally, there is no such entity as a biotechnology industry. Rather, it is a broad, enabling technology that impacts on productivity in a wide range of sectors.

The biotechnology community (represented in Figure 1) includes dedicated biotechnology firms, established corporations with a biotechnology division, university departments, research institutes, venture capital firms, regional associations, regulatory authorities and suppliers involved directly or indirectly in biotechnology. Within this community are firms involved in developing and applying both traditional and "new" biotechnology. The innermost circle represents the subgroup of corporations that concentrate on the development of "new" biotechnology products. This "core" group has been the focus of most attention and it is this subsector that has been targeted by countries that regard biotechnology as a strategic area that can contribute to their long-term economic growth.

. . . which can contribute to long-term growth and jobs

Figure 1. Biotechnology Community



Precise data are lacking

It is important to emphasize that reliable data on sales, trade and employment are not available from Statistics Canada, as products derived from biotechnology have not been differentiated within the Standard Industrial Classification (SIC). Studies and directories differ in their definition of biotechnology and tend to include firms that are only marginally involved in the field, making international comparisons difficult. Published revenue figures do not distinguish

between product sales, contract research or income earned from distribution. To gain media and investor attention, many emerging health care companies call themselves biotech firms, even though their products are derived from traditional synthetic or organic chemistry. For these reasons, the size of the "industry" is often overstated. It should also be noted that this is not just a Canadian phenomenon.

2.1 Global Context

Health care accounts for 90% of US$15B in sales worldwide

Current worldwide sales of biotechnology-based products are estimated at around US$15 billion, with human health care accounting for over 90 percent of applications.

Strong science and research base is required

Industries employing biotechnology are concentrated in highly industrialized countries because of the requirement for a strong science and research infrastructure base and for the industrial capacity to convert basic research into products. The United States, with its particularly strong base of university and scientific research, has dominated global markets, especially in terms of sales, employment and R&D. Leading U.S. biotechnology companies completed their initial public offerings in the early 1980s, about a decade ahead of Canadian firms. U.S. industry has also benefited from strong government support for research in biological and biomedical sciences, a greater entrepreneurial culture, a favourable science-based regulatory structure, intellectual property policies that allow for the patenting of higher life forms, its *Orphan Drug Act*, which provides an incentive for research in otherwise unprofitable areas, easier stock exchange listing requirements for young startups, and the existence of a large number of venture capital firms along with several specialized and well-capitalized biotechnology funds.

Countries other than U.S. have few dedicated biotechnology firms

Unlike in the United States, where biotechnology has been largely developed and commercialized by new, specially formed companies, research in other countries is more likely to have taken place within large pharmaceutical and chemical companies as well as in universities and research institutes. The result has been fewer dedicated biotechnology firms. The European biotechnology industry is dominated by large companies such as Institut Pasteur in France, Plant Genetic Systems in Belgium, Glaxo in the U.K. and Ciba-Geigy (recently merged with Sandoz to form Novartis) and Hoffmann-LaRoche in Switzerland. However, smaller dedicated firms are starting to make their presence felt, particularly in the United Kingdom, which accounts for one quarter of European companies, where the easier listing requirements of London's Alternative Investment Market has facilitated the emergence of publicly traded biotechnology businesses. U.S. firms are more concentrated in health care than their European counterparts. Other countries with significant biotechnology sectors include Japan, Taiwan, Australia and Israel.

As shown in Table 1, based on its size, Canada has proportionally more companies in biotechnology than either the U.S. or Europe and in absolute terms, more companies involved in agri-food. Overall, Canada compares very favourably although it is significantly behind the U.S. and Europe in terms of research expenditures per employee.

Canada leads in agri-food biotech

Table 1. International Comparison of Dedicated Biotechnology Firms

	U.S.[a]	Europe[b]	Canada[c]
General:			
Firms (number)	1 287	716	224
Public companies (number)	294	49	59
Total employment (number)	118 000	27 500	11 000
Firms employing fewer than 50 people (%)	33	70	72
Revenue (US$ billions)	14.6	2.2	0.8
R&D (US$ billions)	7.9	1.9	0.3
R&D per employee (US$)	67 000	69 000	27 000
Net profit (US$ billions)	(4.5)	(1.4)	(0.1)
Market segments:			
Therapeutics (%)	42	27	37
Diagnostics (%)	26	17	22
Agri-food (%)	8	11	26
Industry suppliers (%)	15	26	3
Chemical, environmental, other (%)	9	19	12

[a] Ernst & Young, *Biotech 97.*
[b] Ernst & Young, *Europe Biotech 96.*
[c] Ernst & Young, *Canadian Biotech 97.*

The biotechnology industry worldwide continues to experience major losses because of the high costs of R&D and long time period required to commercialize new products. Table 2 shows the losses experienced in 1994 by a sample of the larger firms including those in the agri-food sector, where R&D is less intensive than in human health.

High costs, long time for research delay profitable commercialization

Table 2. Selected U.S. Biotech Industry Finances, 1994

Sector (number of top firms)	Revenue (US$ millions)	R&D (% of sales)	Net profit (US$ millions)
Biopharmaceuticals (22)	4 528	3 055 (67)	(1 538)
Ag-bio (15)	400	85 (21)	(141)

Source: James G. Heller Consulting Inc.

Of the 294 U.S.-based public companies, only 18 percent are profitable compared with 20 percent in Canada. Based on their cash burn rates, Ernst & Young estimates that the median U.S. firm in 1996 typically will survive for 28 months before another infusion of capital is required.

Diagnostic products take 2–5 years and $20M to market, compared with 8–12 years and $150–250M for drugs or crop varieties

The time and costs required to bring a product to market range from two to five years and up to $20 million for an innovative diagnostic product, and from eight to 12 years and between $150 million and $250 million for a new drug or crop variety. In the bio-pharmaceutical area, for example, given the high level of R&D investment (some US$15 billion over the past 15 years), sales and payback to date have been disappointing, but the prospects of high returns continue to entice investors. (Amgen Inc., the most successful biotechnology company, has had an average return on assets of some 30 percent, with a cumulative cash flow of US$1.7 billion for the three years ended December 31, 1995, on corresponding revenue of US$5 billion.)

Strategic alliances are needed to spread costs, reduce risks

Strategic alliances with large multinational companies have become essential in order to share these high costs and risks and to tap into the managerial and regulatory expertise, marketing strengths and manufacturing capabilities of their larger partner. (In 1995 in the U.S., the pharmaceutical industry replaced the stock market for the first time as the principal source of funding for biotechnology firms.) However, most alliances tend to involve companies in the health sector, as the pharmaceutical industry worldwide is seeking access to new technologies to offset fierce price pressures and dwindling internal product pipelines. In return for this support, biotechnology companies have to give up substantial portions of their equity and control over manufacturing and marketing strategies. While North America and Europe have traditionally emphasized early-stage agreements, Asian companies tend to focus on deals involving products in clinical trials or near to market. The earlier such financing takes place, the more rights are ceded.

Pace of regulatory approval has major influence on speed of access to new products in various countries

In addition to high R&D costs, a factor affecting profitability is the international regulatory environment. Overly stringent or poorly defined approval requirements can unduly delay the introduction of new products and add to testing and reporting costs. The regulatory approval system for therapeutics and diagnostics is generally more expeditious in Europe than in the U.S., which has led to increased U.S. investment in Europe and has allowed European patients to gain earlier access to various new medical technologies. For genetically engineered agri-food products, the U.S. has a highly streamlined, predictable and transparent approval process relative to both Europe and Japan, where difficulties in obtaining regulatory approvals for agricultural products derived from biotechnology continue to exist. For example, the European Union (EU) has only recently approved, amidst much controversy, the importation of genetically engineered canola, corn and soybeans.

While there is no formal mechanism under the North American Free Trade Agreement (NAFTA) and the World Trade Organization (WTO) for the mutual acceptance of regulatory approvals, international negotiations regarding harmonization of test protocols and acceptance of data are under way in a number of forums. This may not necessarily result in mutual recognition of regulatory decisions, but should reduce the costs incurred by companies that must meet data requirements in a number of jurisdictions (see Annex C — *Regulatory Policies* for a fuller presentation of regulatory policies internationally).

Harmonization of test protocols may reduce costs to meet regulatory standards

2.2 North American Context

The United States has a pre-eminent position in biotechnology, not only as a manufacturer but also as the major market and source of investment. A significant challenge for seeking entry into the market is meeting the stringent requirements for health care products set by the U.S. Food and Drug Administration (FDA).

U.S. leads in biotech manufacturing and investment

Mexico has no explicit biotechnology strategy. There are no major impediments to the importation of biotechnology-derived products, but the market potential is relatively small.

Mexican market potential is small

In contrast to the U.S., Canada and Mexico deny patent protection to higher life forms such as newly created varieties of plants and animals. NAFTA does not currently require Canada to patent higher life forms. However, members of the WTO are obligated to review the patentability issue four years after the date of entry into force of the WTO agreement; the review is scheduled to take place by January 1, 1999.

Higher life forms are not patentable in Canada or Mexico

2.3 Canadian Industry Snapshot

In Canada, as in other countries, biotechnology has not lived up to initial optimistic forecasts. Most biotechnology firms have no product sales and are losing money, as commercialization has been slower than expected.

Commercialization is slower than expected

Industry Structure and Importance

A study by James G. Heller Consulting Inc. (*Background Economic Study of the Canadian Biotechnology Industry*, Toronto, 1995) estimates that the Canadian biotechnology "community" (i.e. the outer ring in Figure 1) numbered about 530 organizations employing approximately 23 000 people in 1993. Of this, the group involved in developing and applying both traditional and "new" biotechnology contained about 300 companies employing 10 000 people. The segment whose business is substantially "new" biotechnology (i.e. the innermost ring in Figure 1) was

"New" biotech firms number 147, employ 7 200 people in Canada

estimated to consist of 147 firms employing 7 200 people. Revenue of this core group was estimated at $465 million (88 percent health care) with exports of $109 million. (The more recent Ernst & Young survey, summarized in Table 1, indicates that Canada's core biotechnology sector has grown since 1993, and also provides a consistent method of comparison with the U.S. and Europe.)

The Heller study indicates that in 1993 the biotechnology community (i.e. all organizations embraced in Figure 1) accounted for 0.17 percent of GDP, 0.19 percent of total employment and 0.92 percent of all new investment. These numbers do not take into account the *potentially* large spillover benefits on key sectors of the economy through biotechnology R&D such as health, agri-food, forestry and environment.

Most firms are very small

Of Canada's core industry, most are very small, with 57 percent of the firms having fewer than 10 employees and two thirds having fewer than 20 employees. In contrast to previous years, Quebec now accounts for the greatest proportion of companies (40 percent) followed by Ontario (27 percent) and British Columbia (17 percent). The largest number of ag-bio-tech firms is found in the Prairies, particularly Saskatoon, clustered around the University of Saskatchewan and the National Research Council's Plant Biotechnology Institute.

Most firms are privately held, Canadian-owned but with high degree of foreign influence through alliances

Most biotechnology firms are privately held. The *Canadian Biotechnology 1996 Directory* (Contact International Inc., Georgetown, Ontario) lists 33 public companies in the *narrowly defined* industry (a quarter of the actual biotechnology firms), of which over two thirds focus on human health. Only about 10 percent of the core industry is foreign controlled, but this figure understates the extent of foreign influence. Connaught Laboratories, for example, which is now owned by Pasteur Merieux of France, is the largest biotechnology company in Canada. In addition, multinational drug companies have entered into alliances with Canadian bio-pharmaceutical firms, acquiring exclusive worldwide marketing and manufacturing rights to Canadian products at a relatively early stage in development. This degree of control over production and marketing will make it difficult to establish a significant domestic manufacturing industry.

Regional associations pursue local interests

In addition to Connaught, major Canadian-based companies include Allelix Biopharmaceuticals, Biochem Pharma, Cangene, Hemosol, Biomira, Spectral Diagnostics and Alta Genetics. The Industrial Biotechnology Association of Canada (IBAC) represents some 35 companies focussing on advocacy issues relating to regulations, public awareness and R&D policy. A number of regional biotechnology interest groups exist across Canada, each concerned with promoting the interests of their members. Most firms are not members of IBAC, preferring instead to work

with their local regional groups. These regional organizations participate in IBAC, and the association has started to define a working relationship with them. In addition, the Canadian Institute of Biotechnology is involved in networking and general promotion (see Annex E —*Key Firms and Associations*).

Products and Markets

Canadian revenue derived from biotechnology products and services is estimated at around $800 million (Table 3). Most activity consists of classical biotechnology.

Canadian biotech revenues top $800M

Table 3. Sales by Category[a], Canadian Biotechnology, 1996 Estimates

Area	Products/services	Sales
		($ millions)
Human biologicals	• vaccines	250
	• blood products	50
Total		**300**
Human diagnostics	• tests	40
	• supplies	56
Total		**96**
Agri-food	• plant breeding	127
	• biological control	9
	• animal vaccines	1
	• animal genetics	48
	• feed additives	30
	• food science	4
	• diagnostic tests	5
	• enzymes, yeasts	95
Total		**319**
Aquaculture	• vaccines	7
	• tests	2
	• brood stock genetics	25
	• product extraction	8
	• services	17
Total		**59**
Environment	• bioremediation	**38**
All areas		**812**

[a] Some categories like diagnostics include significant amounts of imported products for redistribution.

Source: Contact International Inc., *Canadian Biotechnology 1996 Directory*, Georgetown, Ontario.

Traditional vaccines dominate Canadian-produced human health biotech

Human health is the major focus, with vaccines accounting for a high proportion of Canadian product sales. However, the current contribution of second-generation biotechnology to sales is still limited, as much of these are conventional vaccines based on killed pathogens or toxins rather than recombinant proteins. Other than vaccines and certain blood products, no bio-pharmaceuticals are yet manufactured in Canada, although over 80 are in the product development pipeline. Bio-pharmaceutical imports in 1995 are estimated at $85–100 million.

Most diagnostics imported with Canadian firms focussed on selected niches

The diagnostic laboratory market is composed of capital equipment such as general chemistry analyzers, disposable and reusable labware and reagents, chemicals, and test kits, used by blood banks, hospitals and private laboratories. Based on a number of surveys, the Canadian market is estimated at around $250 million, with over 90 percent of products imported. Biotechnology-based diagnostic products (i.e. using antibodies and antigens to detect hormones, proteins, viruses and bacteria) are concentrated in the **immunodiagnostics** subsector. Among the products marketed by Canadian firms are tests for drug monitoring, cancer tumor markers, sexually transmitted diseases, autoimmune diseases, monitoring of metabolic disorders and cardiac markers. Canada also produces a wide range of infectious disease antigens used by manufacturers of immunoassay kits worldwide, as well as enzymes and reagents used in clinical chemistry.

Few genetically engineered plant products have reached retail market in Canada

In **agri-food**, most revenue comes from the sale of yeast strains and lactic bacterial cultures and animal genetics (bull and dairy semen and bovine embryos). Although some 20 genetically engineered crops such as tomatoes, potatoes, canola, corn, soybeans and flax were approved for sale in Canada, with the exception of canola (1995 market introduction), soybeans, potatoes and corn (1996 market introduction), most transgenic plant products have not yet reached retail shelves.

Traditional and genetic technologies are growing in response to rising aquaculture in Canada

Aquaculture biotechnology supports Canada's $350-million aquaculture industry with such traditional technologies as hormonally induced spawning, hormone administration to induce sex change for growth acceleration and improved food conversion, vaccine production and extraction of industrial compounds from marine organisms through physical/chemical techniques. Newer techniques include gene transfer to produce faster-growing and healthier fish, frozen storage of genetic material (cryopreservation), stock identification using DNA sequences and development of rapid tests to identify diseases. Most of the industry's sales consist of first-generation vaccines, conventional fish feed and marine-derived products and technical services for genetic improvement and environmental cleanup. In the area of embryo and gamete selection, monosex manipulation techniques are widely utilized to create faster-growing fish. Canadian researchers

have considerable expertise in triploidy (a process that inserts an extra set of chromosomes into eggs to create a sterile species with higher growth rates) and in the development of transgenic salmon with genes for superior growth. However, domestic regulations governing containment of transgenic species and the long lead time involved in breeding viable offspring with this trait have discouraged Canadian commercialization in this area. Instead, this technology is first being licensed to offshore hatcheries, which will have negative consequences for the Canadian aquaculture industry. In the area of aquatic bioprocessing (obtaining valuable compounds from marine organisms), domestic commercial activity is limited.

Small domestic and large international firms target bio-remediation to restore contaminated sites

Besides composting and the classical applications of biology in the treatment of municipal and industrial wastewater, firms in the Canadian bioenvironmental sector are involved in **bioremediation** of hazardous wastes, with some activity in biological gas cleaning and production of microbial biosensors for detection of toxic compounds. The market is served by two types of companies: small specialized bioremediation firms who generally lack the resources to establish a local presence offshore, concentrating on projects within Canada and nearby U.S. states; and large engineering consultants and contractors who offer a wider range of cleanup options and who have a competitive advantage in accessing international markets. Bioremediation firms tend to target petrochemical companies and petroleum distribution outlets and government departments with contaminated sites, while engineering consultants target the large pulp and paper and mining industries as well as government.

Forest biotech relies on federal government funding

Forest biotechnology activities in Canada are mainly undertaken by the federal government and focussed on research such as forest regeneration techniques, forest protection, wood preservation, pulp biobleaching, and treatment of pulp and paper mill effluent. The industry is conservative and slow to implement new technologies. Major issues facing forestry are related to sustainable development and the conservation of old growth forests. Land tenure (provinces own most forest resources) and intellectual property concerns (patents may expire before genetically improved trees are ready for harvesting) influence commercial development of biotechnology.

Biotech is not yet competitive with current technologies in many areas

Although Canada is not a major player in animal vaccines and industrial enzymes, it has a few promising firms in these areas. In most other areas — including fuel, bulk chemical production, and mineral extraction — biotechnology is not competitive with current technologies.

Human Resources

Industry relies on highly skilled human resources in leading-edge technologies

Highly skilled scientists, engineers and managers with expertise in fields such as molecular biology, protein chemistry, immunology, computer modelling, bioprocess engineering, quality control and regulatory affairs are required to translate basic science into proprietary technology and to establish production and marketing capability.

A recent study for Human Resources Development Canada by the Paget Consulting Group (*Building Long-term Capability Now: Canadian Human Resource Study in Biotechnology*, Mississauga, Ontario, May 1996) indicates that the industry currently employs some 8 000 people. Approximately 40 percent are involved in basic and applied research in areas such as gene therapy, DNA amplification, rational drug design and carbohydrate chemistry. At the other end of the technology spectrum are the industrial bioprocessing techniques of fermentation, and downstream recovery and purification. Aside from Connaught, however, most Canadian firms have not yet brought a manufactured product to market, so there is a shortage of people with bioprocessing capability and regulatory experience, and these skills must be imported. Without ready access to skilled people and the facilities in which the commercial products will ultimately be produced, successful development and production scale-up is difficult to achieve. Apotex/Cangene recently announced that its expanded Winnipeg fermentation facility, designed to meet U.S. FDA current good manufacturing practice (cGMP) requirements, will be available for contract manufacturing.

Few firms have brought manufactured products to market or have human resources to do so

Policy Framework

Generous government R&D tax incentives give Canadian firms important cost advantage

A number of general policies are of particular importance to biotechnology firms. One of the most important is Canada's R&D tax incentives, which are generous in comparison with those available in other countries. The after-tax cost of $1 of R&D is $0.69 in Canada versus $0.89 in the U.S., for example. Given the industry's dependence on R&D, this provides Canadian firms with an important competitive advantage. However, the incentive for Canadian public companies as well as foreign firms is reduced by the non-refundable nature of the credit.

Most biotech-derived substances will continue to be regulated under current Acts

In the area of regulations, Health Canada regulates bio-pharmaceutical drugs, diagnostics and novel food products and processes under the *Food and Drugs Act*. Agriculture and Agri-Food Canada is responsible for novel feeds under the *Feeds Act*, novel microbial supplements under the *Fertilizers Act*, veterinary biologics under the *Health of Animals Act* and all plants with novel traits, including trees, under the *Seeds Act*. In a practical approach supported by industry, most biotechnology-derived products will continue to be administered by existing legislation and regulatory agencies. The exception will be products not covered under other federal legislation, which will be regulated by Health Canada and Environment Canada under the *Canadian*

Environmental Protection Act (CEPA). The New Substances Notification Regulations, recently published and which came into force on September 1, 1997, establishes requirements for "new" substances (i.e. all substances not contained on The Domestic Substances List). Companies are now required to perform a pre-import or pre-manufacture notification and assessment of all new substances that are products of micro-organisms to ensure "toxic" substances are not introduced into the Canadian marketplace. Products that are subject to the regulation are those biochemicals, biopolymers and organisms not covered by other federal legislation. These include products used in applications such as bioremediation, mineral leaching and energy production.

NBS set up biotechnology networks, higher levels of research, and a research institute

In addition to the above policies, the federal government's National Biotechnology Strategy (NBS) focussed specifically on this sector. Introduced in 1983 through the Ministry of State for Science and Technology, the aim of the NBS was to ensure that Canada realizes the potential of biotechnology by initially focussing R&D on certain strategic areas (human and animal health, nitrogen fixation and plant strain development, cellulose utilization and waste treatment, and metal recovery and mineral leaching), ensuring an adequate supply of highly trained personnel, encouraging research collaboration, and creating a climate conducive to investment. A National Biotechnology Advisory Committee and an Interdepartmental Committee on Biotechnology were created to monitor and support this initiative. Fruits of this policy include the establishment of a number of biotechnology networks, an increased level of biotechnology research activity in government departments and the creation of the Biotechnology Research Institute in Montreal. Work is continuing on other areas such as human resources development and speed of product commercialization. The last comprehensive review of the NBS was undertaken in 1991. A task force has been created to coordinate the development of a new strategy, the Canadian Biotechnology Strategy (CBS). The CBS, to be ready in mid-1998, will also reflect new needs to be addressed such as public acceptance of biotechnology-derived products and ethical and social issues.

New CBS will be ready by mid-1998

2.4 Performance and Competitiveness

Performance

Revenues grew rapidly by 24% a year

The biotechnology industry has grown rapidly between 1989 and 1993 (Table 4). For the broad group, revenue grew by 24 percent a year, and exports doubled. Notwithstanding this performance, Canada has a growing trade imbalance in diagnostics and bio-pharmaceuticals.

Table 4. Key Statistics for the Canadian Biotechnology Industry

	1989	1993
Employment		
Number	13 800	23 200
Share of total manufacturing (%)	0.11	0.19
Investment		
Value ($ millions)	121	221
Share of total manufacturing (%)	0.40	0.92
Exports ($ millions)	374	748
Imports ($ millions)	147	430

Source: James G. Heller Inc., 1995.

High revenues are surpassed by higher R&D expenses

R&D expenditures for the subgroup of 147 firms involved in "new" biotechnology increased from $215 million in 1989 to $332 million in 1993. More than three quarters of R&D spending went toward health care. However, the financial results of this group were poor. In 1993, only one biotechnology firm had positive net income, while Canada's senior public biotechnology companies (all health care) experienced a combined loss of $69 million on revenues of $60 million.

Competitiveness

New biotechnology is based on recombinant DNA, DNA amplification, cell culture, cell fusion, rational drug design and other various disciplines of molecular biology. These offer little competitive advantage by themselves, as they are available to competent researchers around the world. Further, much of the scientific expertise in Canada resides in universities and government laboratories. There is less crossover into industry than in the U.S., as Canada does not have the same level of receptor capacity.

Firms compete on intellectual property

Relative to most other fields, biotechnology companies do not compete on production costs, but rather on intellectual property. Without legal access to a proprietary marketable technology, commercialization cannot occur and investment capital will not be forthcoming. While a firm may be able to license the necessary technology, when it is available, the royalty load can dramatically increase product costs. Also, restrictions usually incorporated in licences with respect to product applications, territory, etc., can also reduce profitability. Firms are therefore under pressure to develop in-house capacity for innovation and new product development.

As few second-generation products have been commercialized, comparison of production costs at this time is not possible. In any event, process economics are more important for products whose patents begin to run out, for high-volume products such as insulin and industrial

enzymes and for environmental applications, where different cleanup options are evaluated in terms of costs and efficiencies.

Developers of therapeutics often contract out production to focus on core competencies

Unlike other manufacturing sectors that strive for continuous process improvement, regulatory requirements for therapeutics make it difficult to implement any significant changes to manufacturing processes after a product has been approved for sale, because of concerns that the product may differ from that produced by the original process. A manufacturing change would precipitate a requirement for a new regulatory review, resulting in a marketing delay. Because firms are under intense pressure to get a product into clinical trials, contract manufacturing is often employed as an alternative strategy to in-house production, allowing companies to focus on their core competencies. A major problem facing Canadian bio-pharmaceutical firms is the lack of production facilities compliant with good manufacturing practices (GMP) regulations in Canada. If Canadian biotherapeutic firms are unable to develop or contract domestic manufacturing capability on acceptable terms, their competitive position could be impaired.

Canadian firms spend less on R&D per employee

Research costs are lower in Canada because of generous R&D tax credits and lower labour costs. While R&D expenditures have increased significantly, Canadian firms appear to spend substantially less than their U.S. or European counterparts per employee, as indicated in Table 1. These differences may be partly due to the fact that Canadian and European firms are at an earlier stage of development, but they are troubling nonetheless. Also of concern is the strong net outflow of U.S. intellectual property to European organizations (more than 300 biotechnology deals took place between 1992 and 1995), which could enhance Europe's competitive position.

Most agri-food R&D is conducted in government labs and universities

Canada has established strong capability in a number of areas, notably biomedical and agricultural research. To date, this has resulted in Canada's emergence as a leader in both canola and cattle genetics, where a number of genetically-engineered varieties have been commercialized successfully. Despite Canada's research excellence, it continues to be several years behind the U.S. in developing industrial applications and commercialization. In the Canadian agri-food sector, much of the R&D capability is located in government laboratories and universities. Most Canadian research in plant breeding is focussed on oil crops (canola, soybeans) and cereals (corn, wheat). However, this is a crowded research field, with key patents relating to herbicide and insect tolerance controlled by foreign multinationals who have not provided exclusive access of their technology to any one seed company. There are no Canadian-owned, research-based seed companies. Most of the smaller dedicated ag-bio-tech firms in North America have ceded ownership to large chemical and agricultural corporations such as Monsanto, DowElanco and Pioneer, so this sector holds little promise of growth for startup biotechnology companies. Also, it is troubled by issues different from those facing bio-pharmaceutical firms, notably lower returns on capital and a lower level of consumer acceptance.

In aquaculture biotechnology, Canadian strengths include vaccines for fish and shellfish as well as genetic characterization to support brood stock optimization. However, most of the work is based on conventional biotechnology rather than on genetically modified organisms.

Canadian firms have a reasonably strong base of experience in soil bioremediation and in the design and construction of wastewater treatment plants, but this expertise is not strong enough to differentiate the sector from international competitors.

3 CHANGING CONDITIONS AND INDUSTRY RESPONSE

3.1 Evolving Markets

Multinationals dominate, but Canadian firms hold niche markets

Canadian firms have begun to carve out a number of important niches. They are about to bring to market new drug therapies for certain cancers and neurodegenerative diseases, bone disease and viral infections. Although there is a great deal of research in gene therapy, most of the activity is conducted in hospitals and universities, as few companies have been established in this area. Several companies have established a presence in the immunodiagnostics area, which is the only diagnostic subsector worldwide forecasted to have strong growth rates close to 10 percent a year. However, the market is dominated by multinationals, and cost containment and cost effectiveness issues worldwide make it a difficult business in which to thrive.

Health of cattle supports Canada's reputation in genetic selection

Transgenic plant agricultural products came on to the Canadian market in 1995. In the animal area, genetic selection through advances in semen collection and new reproductive techniques such as embryo sexing, *in vitro* fertilization and artificial insemination are transforming animal breeding programs and providing significant market opportunities. Canada is second only to the U.S. in exports of semen and embryos as a result of this country's reputation for the health of its cattle. The major issue facing the agri-food industry is consumer acceptance. While the industry still considers the approval requirements to be demanding, the regulatory process can be said to be beneficial if it reassures consumers of the safety of products derived from ag-bio-tech.

Bioremediation costs less, treatments are more environmentally acceptable than conventional means

Environmental biotechnology in Canada or elsewhere has not shown the same degree of rapid development as health care or agri-food. Unlike in these sectors, environmental applications do not result in the production of high-value products and depend on trade secrets, not patents, for intellectual property protection, so venture capital has not been as forthcoming. However, **bioremediation** of hazardous wastes is a rapidly growing market segment in Europe and the U.S. because biotechnology is often less costly and more acceptable than conventional treatments such as incineration. Most Canadian firms involved in bioremediation generally do not have technologies unique from their competitors or the resources to establish an offshore presence. The fact that the environmental business is service-oriented means that opportunities to generate international business without a local presence are limited. Other major impediments are the lack of scientifically validated accreditation criteria to confirm process efficacy and the lack of demonstration sites for long-term experimentation, technology development and process verification under actual field operating conditions. This would stimulate wider use of the technology by overcoming the "black box" nature of bioremediation.

Aquaculture has promising markets for biotech

In aquaculture biotechnology, there are promising markets for rapid pool-side diagnostic tests and second-generation fish vaccines, particularly for shrimp, in conjunction with training programs in good animal husbandry practices, so that farmers in developing countries are educated to optimize production techniques.

3.2 Financing

Growth of venture capital funds and TPC ease access to financing

Firms need substantial capital because of the research-intensive nature of biotechnology and the long time required to bring a product to market. Companies survive and grow on the success of their R&D efforts. While access to capital was traditionally regarded as a major impediment, present evidence suggests that, with the possible exception of small, early-stage companies, this problem has diminished in importance with the growth of the public and private equity markets. At one time, MDS Health Ventures was the major source of investment capital, but Canadian biotechnology companies have benefited from the emergence of a number of tax-supported venture capital funds such as the labour-sponsored Canadian Medical Discoveries Fund, whose mandate is to invest in early-stage biomedical research. In addition, the federal government's new Technology Partnerships Canada program offers financial support for innovative technologies at a near market stage of development.

Strategic alliances are important avenue of support

Strategic alliances with multinational corporations have also enabled Canadian firms to obtain needed support but, as in other countries, most alliances are with pharmaceutical firms, with resulting loss of control over manufacturing and marketing strategies.

Access to public equity capital increased greatly in 1996 but now is becoming more costly, difficult to obtain

Between 1991 and 1995, investments in Canadian biotechnology amounted to $1 billion, with private placements/venture capital accounting for 39 percent, initial public offerings 27 percent and public offerings 31 percent. Human health care accounted for 88 percent of the investment, followed by agriculture at 9 percent. In 1996, as a result of the strong public equity market, the industry raised over $1 billion, but the window of opportunity has narrowed so that equity capital now appears to be more costly and more difficult to obtain. As in previous years, most of this capital infusion is concentrated in health care.

Earnings on stocks may be long time in coming

Biotechnology stocks are volatile and are not valued as most other issues. Until a biotech company starts selling a viable product, its stock price is dependent on its research results. With expectations of earnings in the distant future, more subjective measures are used, such as how far the firm is in its clinical trial program, the clinical results to date and partnerships with large pharmaceutical companies, which are an indication of the viability of the emerging technology.

Disappointing clinical results for one company may dampen investor confidence in others. Canada has only a handful of analysts and investors with expertise and interest in biotechnology, so conferences and other networking activities are important in linking investors and entrepreneurs. The more established publicly traded firms do not have as severe a problem, but it is important for them to keep the U.S. investment community aware of Canadian technical developments. Because of past clinical failures, investors now look for firms with more than one promising drug in trials and are particularly attracted to those companies that have a platform technology that can be used to develop a range of products.

Biotech investors shop warily

3.3 Investment

A strong research infrastructure base, quality of technical personnel and overall cost per researcher are the most important factors influencing location of R&D investment. Although strong patent protection is also often cited as being just as important, it has always been difficult to determine precisely the relationship between intellectual property and investment. A study published by the World Bank in 1993 (Edwin Mansfield, *Intellectual Property Protection, Foreign Direct Investment and Technology Transfer*, Discussion Paper 19, International Finance Corp., Washington, D.C.) indicates that a country's intellectual property protection affects the type of investment in question (e.g. sales and distribution, rudimentary assembly/packaging, complete manufacture, or R&D facilities). Many of the firms studied tended to regard strong intellectual property protection as being more important in decisions regarding transfer of technology than investment in manufacturing facilities.

Intellectual property protection has strong influence on type of investment decisions

The *Patent Act Amendment Act, 1992* (commonly referred to as Bill C-91), which eliminated Canada's compulsory licensing system for drug patents and established exceptions to patent infringement for the purposes of regulatory approval, has encouraged multinational pharmaceutical companies to increase their Canadian R&D investment. The Patented Medicine Prices Review Board (Newsletter, Vol. 1, Issue No. 1, July 1997) reports that R&D as a share of industry sales increased to 12.3 percent in 1996 from 6.5 percent in 1988. This is well in excess of the commitment to reach and maintain an average R&D-to-sales ratio of 10 percent that was undertaken by brand-name pharmaceutical companies following the 1993 cessation of compulsory licensing. However, much of the research is conducted at universities and teaching hospitals and could be considered footloose. Of the $665 million spent on R&D, approximately 78 percent went toward preclinical and clinical trials and drug regulatory submissions, while basic research accounted for 22 percent of the total. In addition to the stimulus from Bill C-91, R&D investment has been encouraged by the quality of Canada's research, research tax advantages and capability in conducting clinical trials.

Canadian R&D investment nearly doubles with cessation of compulsory licensing

Level of government support often affects location decisions

Once a firm has narrowed its choice to a handful of sites with similar advantages, government incentives such as attractive tax credits, low interest loans, grants and land and facility offerings can be crucial. Bio-Intermediar, for example, located its North American operations in Montreal because of substantial government support; another important factor was the presence of the National Research Council's Biotechnology Research Institute, around which a cluster of bio-pharmaceutical firms had formed, which was a source of potential customers for this Netherlands-based firm.

Sales in non-U.S. markets can finance costs of meeting U.S. regulatory compliance

Manufacturing outside the jurisdiction of the U.S. FDA is another major commercialization strategy followed by both U.S. and foreign companies. This allows them to enter significant non-U.S. markets at a lower regulatory cost, thereby generating revenues to ultimately afford the burden of proof required for the U.S.

Federal investment strategy seeks to make Canada location of choice for NAFTA investors

Life sciences including bio-industries are a target sector under the new federal investment strategy that seeks to make Canada the NAFTA location of choice for new investment and expansion of existing investment. The general thrust of the investment strategy is to help Canadian small and medium-sized enterprises achieve beneficial strategic alliances, working with Canadian subsidiaries of multinationals to increase research partnerships and, where appropriate, production.

3.4 Human Resources

Skill shortages may leave new jobs created unfilled . . .

Shortages of qualified personnel are expected over the next five years as companies mature and move from early-stage research to commercial production. The Paget study cited above predicts that industry growth will create 4 000 new jobs by the year 2000: of this number, 1 300 will be in research, technical and support activities, 2 000 will be in commercialization and 700 will be in management. Government regulatory agencies also will require additional staff to handle the growing demand for new product approval.

. . . especially in specialized research areas

Universities and community colleges should be able to meet the demand for scientists and technicians with general skills. Shortfalls are expected in specialized research areas such as peptide chemistry, gene therapy and bioinformatics plus production scale-up, formulation, regulatory affairs and international business management. The study recommends a number of solutions: the strategic use of immigration to acquire needed specialists, a priority list of occupations with "search waived" status and simplification of the immigration process including work permit policies for spouses, development of a regionally focussed training strategy to pool the resources of firms in regional biotech clusters, and the creation of a Biotechnology Sectoral Human Resource Council to act on the study's recommendations.

3.5 Trade

For Canadian firms in the health care sector, trade prospects will be greatly influenced by whether they can meet stringent U.S. FDA requirements. Agri-food products based on biotechnology do not face the same regulatory difficulties. However, this is not the case in Europe and Japan, where guidelines for the introduction of recombinant agri-food products are under development.

3.6 Consumer Concerns

Many consumers are unaware of risk assessment procedures for genetically engineered foods

Consumers are increasingly influenced by broader moral and ethical concerns related to the use and future application of biotechnology, such as privacy related to genetic testing. Consumer awareness of biotechnology is low and is a particular challenge in agri-food. Questions have been raised about the merits and risks of genetically engineered food over conventional products. Some people believe there are no commonly accepted risk assessment protocols or testing guidelines, as there are for human health products. Others believe that while manufacturers may reap substantial economic benefits if their product succeeds, it is likely that the far larger costs of any negative environmental or human health impact will be borne by society.

Transgenic fish may pose problems for other species

Monsanto's recombinant bovine somatotropin (rBST), a hormone associated with enhanced milk production, has met stiff consumer resistance in many markets because of public fears about the consequences of hormones in milk. The continuing scientific dispute whether rBST increases the potential for mastitis (udder infection) also does not inspire confidence. Similarly, there are concerns that the advantageous traits in transgenic plants (e.g. herbicide tolerance) will be transferred to wild, weedy relatives by cross-pollination and that their widespread release may have potential long-term ecological effects that cannot be predicted from short-term, small-scale trials. Crops engineered with *Bacillus thuringiensis* (Bt) genes to produce their own supply of this natural toxin may result in the evolution of Bt resistance among pests, making existing Bt foliar spray products less effective. In many U.S. southern states, fields of Bt-engineered cotton have succumbed to an unusually severe attack of the cotton bollworm, necessitating the use of conventional chemical spraying. The U.S. Environmental Protection Agency (EPA) recently restricted sales of a new Bt-producing corn to states that do not produce cotton because several insect pests migrate between the two plants. This restriction is currently being appealed. The U.S.-based Union of Concerned Scientists has asked the EPA to suspend Bt cotton sales. Transgenic fish escaping into the wild could affect the gene pool of wild stocks, affecting their ocean survival rates, larger appetites, behavior patterns and resistance to parasites and pathogens. Whether such fish can survive in the wild remains unclear. Ongoing research is needed to assess the validity of these concerns.

Informed consumer choice relies on full information, including labelling

Consumers have expressed a desire for more information on products and the ability to exercise choice in the marketplace. Mandatory labelling of new food products that result from genetic engineering is a major subject of public debate, but the added cost and complexity of segregating biotech food products during shipping, storage, processing and packaging would preclude such products from achieving any significant market share. Further, enforcing labelling rules would be difficult, as no tests have yet been commercialized that can confirm whether a food is genetically engineered or not. Communication to consumers on the effectiveness of Canada's regulatory system could address the above concerns and build confidence in biotechnology-derived products. Further study can help identify how consumer confidence can be raised and the type of information needed to meet consumer needs.

3.7 Regulations

Regulatory approval times affect registration costs and speed to market

Canadian regulatory requirements for health care products are similar to those in the U.S. One major difference is that Canada, unlike the U.S., has allowed exports of medical devices prior to their Canadian regulatory approval. However, this advantage to Canadian industry has been reduced as a result of recent policy changes proposed by the U.S. FDA. In the area of approval turnaround time, Canada is significantly faster than the U.S. for diagnostics but is sometimes slower for new biologics because of lower regulatory resources. The Pharmaceutical Manufacturers Association of Canada in its 1996–97 annual review states that the approval time for new drug submissions (separate figures were not available for biologics) amounted to 682 days in Canada, compared with 576 days in the U.S. and 480 days in the U.K. To expedite its drug review process, the U.S. FDA's cost recovery fees raised through user charges for drug submissions are being employed to hire additional reviewers. Health Canada's plan to implement similar user fees is of concern to Canadian industry. Companies believe most of the funds raised should go toward improving regulatory efficiency; otherwise it will be viewed as an additional tax burden and could result in the later introduction of new products in Canada than in other countries.

For agri-food products, the U.S. has less restrictive regulatory hurdles regarding field trials of transgenic plants or to the commercial introduction of ag-bio-tech products. Also, the speed of registration for veterinary biologics, biological pesticides and microbial supplements has usually been faster in the U.S., but the gap has narrowed.

A benchmarking study comparing the time frame and costs required to achieve regulatory compliance for health and ag-bio-tech products in various jurisdictions may be useful, as it could quantify Canada's advantages in attracting investment or highlight areas where improvements are warranted.

Comparison of registration times and costs could attract investment

Current commercial applications of bioremediation are based on the use of naturally occurring micro-organisms. The use of genetically engineered organisms has been restricted in all countries because of concerns related to the effects of their release. The CEPA New Substances Notification Regulations for Microorganisms may involve cost increases for Canadian companies undertaking *ex situ* bioremediation work:

CEPA regulations seek increased safety but may increase compliance costs

- The CEPA regulations cover the importation and production of both genetically modified and naturally occurring organisms. (Corresponding U.S. and European regulation do not apply to natural organisms.)
- "Manufacture" is broadly defined, imposing reporting requirements on firms that promote the growth of natural micro-organisms by removing them, or the soil containing them, from their natural environment.
- Under the CEPA New Substances Notification Regulations for Microorganisms, Canada has been divided into a number of distinct ecozones whereas, under corresponding U.S. EPA regulations, the continental U.S. is considered as one ecozone. This could place Canadian environmental firms at a disadvantage, because separate evidence would be required for each site deemed ecologically distinct.

It is not yet clear how the provincial authorities, who have responsibility for use rather than importation and manufacture *per se*, will choose to regulate bioremediation applications. A significant advantage of the CEPA regulations is that risk assessments of all new bioremediation products subject to them will be consistent, avoiding the possibility of different standards in different parts of the country. If provincial and municipal jurisdictions choose to "piggyback" their safety assessments on the results of the CEPA process, the costs to companies could be minimized. Assurance of a sound and consistent safety assessment process will promote a sustainable industry.

CEPA will ensure consistent risk assessment of new products

3.8 Technology

New technologies transform drug discovery research

In the therapeutic area, a number of new technologies are coming together to transform drug discovery research: genomics (identifying genes involved in a disease and then designing drugs that interact with the gene's processes or their receptors through rational drug design), combinatorial chemistry (rapid synthesis of thousands of compounds constructed from combinations of smaller molecular units such as sugars, amino acids and nucleotides), bioinformatics (use of computers to acquire, store, analyze and manipulate vast amounts of genetic data), and high throughput screening (robotics to automate sample preparation and assay detection systems).

Novel drug technologies under development include nucleic acid-based therapeutics, glycobiology, transgenic plants and animals

A number of novel technologies under development are a radical shift away from protein-based bio-pharmaceuticals. Nucleic acid-based therapeutics, which focus on blocking gene expression through a number of different mechanisms (antisense, triplex, ribozyme and transcription factor decoy), attempt therapeutic intervention at an earlier stage in the molecular pathway of disease than protein-based therapies. Signal transduction therapy (drugs targeting chemical signals within cells) may rival gene therapy in medical significance. Glycobiology (designing medicines based on carbohydrate/oligosaccharide chemistry) has the potential to create a far larger number of therapeutic compounds than protein chemistry. On the production side, the older protein expression systems based on *Escherichia coli* or yeast may be replaced by insect cells or plant cells for niche applications. Finally, transgenic plants and animals for the manufacture of bio-pharmaceutical proteins represent radically different methods compared with fermentation and mammalian cell culture.

Labs consolidate testing through automated assays

Immunoassays have not kept pace with the demand for automation. Diagnostic tests are usually marketed in a self-contained package or kit consisting of reagent vials, reagent-impregnated strips or slides, test tubes, micro-titre trays, etc., requiring a complex series of reagent additions and considerable liquid handling. The market is moving toward a higher degree of automation as laboratories consolidate their testing in favour of new chemiluminescent and fluorescent-based random access systems that can run an increased number of assays. Other immunoassay technologies in the development stage include new immunosensors, new detection labels and methods that don't require the complex separation, washing and reagent additions of current systems, and micro array assays using silicon chips.

Nucleic acid amplification technologies increase accuracy of immunoassay tests

Immunoassay tests based on antibody/antigen reactions are the most common method used for infectious disease testing but do not hone in on the pathogen directly. They are difficult to use with certain types of specimens and are subject to false positives/negatives. Nucleic acid probe tests provide a direct means of detecting nucleic acid sequences and thus allow detection of the disease at the genetic level. Because the concentration of nucleic acid in a sample is

extremely small, at least 20 different nucleic acid amplification technologies have been developed. The standard is polymerase chain reaction (PCR) but it is not available to most companies developing commercial human diagnostic tests due to licence restrictions. Much of the current assay development is focussed on a narrow range of infectious diseases such as gonorrhea, tuberculosis and human immune-deficiency virus (HIV), resulting in an industry and technology shake-out. Also, commercialization has been slow because existing procedures are expensive, labour-intensive and complex. Widespread clinical use will require adoption of the technologies to automated processes in formats that allow high throughput. (Since the sale of Cangene's amplification technology to Organon Technika in 1995, there are no Canadian firms in this field.)

DNA microchips may revolutionize testing through lower costs, easier use and faster results

DNA microchips that use silicon chips containing a high-density array of DNA fragments to capture and/or amplify specific gene sequences have the potential to revolutionize diagnostic testing. Diagnostics containing DNA chips are potentially less expensive, easier to use and faster than those that rely on DNA amplification technology, enabling technicians to generate real time results in minutes, making them suitable for point-of-care testing.

Commercial genetic tests are not yet available for most diseases

Most genetic testing is performed by researchers or by specialty and reference laboratories that develop their own tests. Despite progress with the Human Genome Project and identification of specific genes associated with certain diseases, few commercial FDA approved tests are available because most genes and genetic mutations associated with diseases have not yet been identified.

Transgenic plant creations rely on spectrum of proprietary technologies

The agriculture realm is dependent on a broad spectrum of technologies to create transgenic plants. The following are some of the most important ones:

- Transformation technologies necessary to insert the gene of interest into plant cells. The soil bacterium *Agrobacterium tumefaciens* is commonly used as a vector. Vectorless methods of gene transfer include electrical stimulation and chemicals such as polyethylene glycol (both make the plant cells leaky so that the genetic material can flow in), and the biolistics gene gun (which shoots high-velocity microprojectiles coated with DNA into the plant).
- Markers (e.g. kanamycin) to identify the transformed cells. Cells containing the kanamycin resistance gene will grow in a culture medium containing high levels of that antibiotic while untransformed cells will not grow.
- Promoters used to control when and where in the organism the gene is turned on (e.g. it is desirable to direct the expression of insect tolerance genes only to tissues eaten by insects, such as leaves). The most commonly used promoter is derived from the cauliflower mosaic virus. Isolation of promoters with varying specificities of expression (e.g. that respond to light, heat and wounds, and that show tissue specificity for seeds, pollen, root nodules and tubers) are being identified.

- Gene silencing technologies (antisense, "Transwitch") needed to suppress or inactivate selected genes from being expressed (e.g. to prevent softening in tomatoes).
- Trait-specific genes that control characteristics such as herbicide tolerance or insect resistance.

However, all commercially interesting transformation methods as well as many commonly used promoters and markers are proprietary, owned by multinationals who license these technologies to seed growers around the world.

3.9 Patents

Litigation is important strategy to protect intellectual property rights

The biotechnology industry worldwide has been characterized by significant litigation involving intellectual property rights. Because patents are a company's most important asset and a single "home run" has a huge profitable upside, firms have a strong interest in maintaining strong intellectual property protection, often employing litigation as a strategy to gain or preserve a competitive advantage. Universities and public research institutions have also become more aware of the value of patents and are more active in seeking and protecting their intellectual property. Disputes are more common than in other fields because biotechnology is a relatively new and complex area of activity, with policy and precedents still being developed. This takes money and more importantly time, since product life cycles are not long. Canadian firms generally do not have the resources to initiate court proceedings or protect their own intellectual property from challenges. This is one of the reasons why early partnering with a deep-pocketed ally is pursued.

Claims for patent protection may overlap, create uncertainty, lead to dispute

A large number of technologies are used in developing a genetically engineered product, which could affect a company's ability to compete. Any firm needing access to these technologies must choose the patentees from which to license, if a licence is available. The ownership of certain key technologies may also be uncertain because of overlapping claims. A number of broad blocking patents issued in the U.S. and Europe have also led to disputes, such as Agracetus's broad patent covering genetically engineered soybean or Gene Therapy's sweeping patent for all methods of *ex vivo* human gene therapy.

Backlogs in issuing patents can set back R&D

Delays in obtaining biotechnological patents are a worldwide phenomenon. This is due to the pioneer nature and complexity of the subject matter and the breadth in the scope of protection being sought by applicants, often leading to long prosecutions to ensure the claims are properly supported. A backlog causes difficulties for those companies seeking to confirm that they do not infringe on competing rights; otherwise their research could be set back several years if another is deemed to have priority. Complications also arise when the coverage claimed in an application is significantly reduced before the patent is issued. The Canadian Intellectual Property Office (CIPO)

currently has nine biotechnology examiners and plans to recruit two additional people in this field to reduce its backlog. It has also initiated conflict proceedings in applications filed prior to October 1989 claiming overlapping subject matter.

U.S. grants patents on higher life forms

The industry has also identified uncertainty regarding the protection available to higher life forms as a problem. One of the most difficult questions raised by biotechnology is whether it is ethically and legally appropriate to extend patent protection to genetic material and higher life forms such as plants and animals. A related issue is the ownership of commercially useful biological materials collected in developing countries for potential exploitation (such as drugs developed from tropical forest plant species). The U.S. granted the first patent on a genetically engineered animal, the Harvard onco-mouse, in 1988. Other animals are now being genetically modified to secrete high-value pharmaceuticals in their milk, and similar work is being undertaken to develop plants that carry therapeutic proteins. Aside from the moral issue, opponents fear that such patents could impede basic research, as researchers will be subject to royalties, agricultural input costs will increase, and entire agricultural markets will be closed to competition. Firms argue that funds would not be invested in such projects without the availability of patent protection to guarantee profitability and that research and commercialization are more likely to take place in jurisdictions with a more favourable regulatory climate. Claims about economic losses and benefits are difficult to prove and merit more careful examination. Industry Canada is currently assessing the role of intellectual property policy in protecting Canada's strategic interests.

CIPO refuses patent claims on multicellular life forms

The Royal Commission on New Reproductive Technologies opposed patents on human sperm, eggs, zygotes, embryos and fetuses. The Canadian Intellectual Property Office permits claims to micro-organisms (i.e. algae, bacteria, fungi, protozoa and viruses) and cell lines but refuses protection for multicellular life forms. The decision by the Commissioner of Patents to reject several claims for the Harvard onco-mouse has recently been appealed to the courts, but it could take several years for this particular issue to be resolved. The WTO and the NAFTA do not currently require Canada to patent higher life forms, but Canada may be subject to pressure from the U.S. on this matter. Canada must develop a policy on this issue for the WTO by January 1, 1999.

Treatment methods are patentable in U.S. but not in Canada, Europe . . . . . could affect gene therapy

Methods of medical treatment are excluded from patent protection in Canada, Europe and many other jurisdictions (because they are regarded as inventions not susceptible to industrial applicability), but are patentable in the U.S. Gene therapies, assuming the treated cells are returned to the host, are considered to be methods of medical treatment and therefore are not patentable in Canada. However, processes to modify the cells outside the body are patentable. Canadian access to gene therapy will depend on the ability to license the relevant process technology (see Annex D — *Patent Issues* for an overview on patentability issues in the U.S. and Europe).

3.10 Sustainable Development

Environmental impacts of biotech may be beneficial where they reduce reliance on traditional chemicals for pest and weed control . . .

Fears that some unintended environmental impacts may result from the use of biotechnology (see above Section 3.6 — *Consumer Concerns*) must be examined within a framework that gives recognition to the potentially important contribution of biotechnology to sustainable development by providing new approaches for understanding and managing the environment. New insect- and disease-resistant plant varieties will allow farmers to reduce their reliance on chemical pesticides and herbicides and improve yields, thereby reducing pressures to bring forests and wilderness under cultivation. The nutritional and processing qualities of crops can be improved. New enzymes can be added to animal feed to increase dietary material while reducing the nutrient content of their waste. New biological treatment processes can reduce environmental hazards and increase the availability of potable water.

. . . may extend growing season, ease pressure on resources and boost productivity

For countries in northern climates, biotechnology can improve the cold tolerance of crops and thus extend the growing season. It can also play an especially important role in addressing the needs of developing countries by helping to alleviate global pressures on agricultural and natural resources. The industry can meet the needs of nations such as Pakistan, India and the Philippines for crops with greater salt tolerance and of African countries for drought-resistant crops. Biotechnology can boost the productivity of global fish farming, which will need to contend with dramatically increasing demands in coming decades to meet a growing population and offset dwindling wild fish landings.

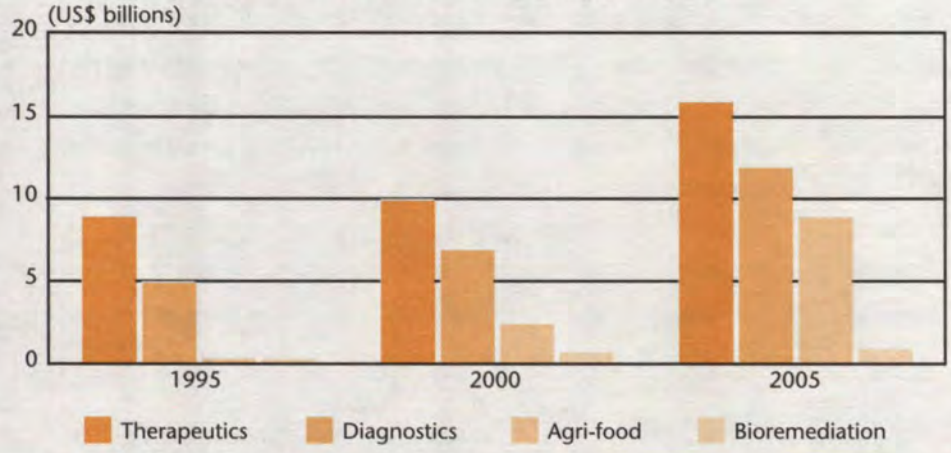
4 GROWTH PROSPECTS FOR THE INDUSTRY

4.1 Demand Outlook

Worldwide sales of biotechnology products/services are expected to increase from their current level of about US$15 billion to US$38 billion by 2005. The strongest growth is projected for the agri-food sector (Figure 2). In this as in other market sectors, the most rapid period of growth is expected to occur after the year 2000.

Worldwide sales are expected to more than double by 2005

Figure 2. Global Biotechnology Market



Source: Based on data from Decision Resources Inc.

For **bio-pharmaceuticals**, sales are expected to grow at only 3 percent a year for the rest of the decade, considerably less than the 10-percent-a-year growth rate this segment enjoyed during the early 1990s. There are fewer than 20 biotechnology-based drugs on the market, six of which account for 80 percent of sales. Although about 300 biotherapeutics are in various stages of clinical development worldwide, accounting for at least 30 percent of all new drugs in the pipeline, few blockbuster drugs are on the immediate horizon. Pressure from governments and insurance payers to keep prices of health care products low will be a major negative impact on market growth around the world. Some analysts contend that bio-pharmaceuticals already on the market, including new approved indications for these drugs, will still comprise the majority of revenue by the middle of the next decade. The major corporate successes are U.S. firms such as Amgen, Chiron, Biogen and Genentech. Hundreds of other firms have as yet failed to produce new drugs with meaningful commercial potential and may end up as little more than contract R&D houses.

Bio-pharmaceutical sales will slow, with fewer major drugs near market . . .

. . . prospects are uncertain for Canadian firms

Diagnostic tests involving antibody/antigen reactions or DNA technology are faster, more sensitive and easier to use than the time-worn procedures of microscopy, culturing of micro-organisms and chemical dyes for the histological staining of cells and tissues. The biotechnology segment of the

Biotech-based diagnostic tests are faster, more sensitive, easier to use, with yearly sales of US$5B growing by 10–15%

in vitro diagnostic market is estimated at around US$5 billion and is expected to grow at around 10 percent a year over the next five years. In certain areas (e.g. tumor markers, infectious diseases, cardiac markers, autoimmunity tests, genetic disorders), sales are projected to grow by around 15 percent a year. Principal factors driving market growth are conversion from low-priced manual methods to higher-priced automated systems, the introduction of new diagnostic marker assays and the recent U.S. FDA ruling that premarket applications may not be required for tumor markers currently in commercial distribution and used for monitoring only, which could speed the market introduction of some tests. The industry is dominated by large multinationals who market automated systems. One of the critical success factors is the size of a company's installed base, as this not only drives profitable reagent sales but also serves as a barrier to competition. Without a unique product, prospects are not encouraging for new entrants or small players such as those found in Canada, as it is an extremely difficult industry in which to compete and thrive. Even with an innovative product, commercial success will depend on a firm's ability either to market low-volume niche products, which are not of interest to multinationals, or to form alliances with these major producers for products that can work on automated systems. The fundamental restructuring of health care delivery such as price pressures and reimbursement cuts, which is occurring on an international level, is exerting a negative impact on the whole diagnostic market. To be successful, tests will need to be novel and cost-competitive, clinically relevant, reimbursable and capable of being run by lower-skilled technicians.

Details underlying the strong projected growth in **agri-food** biotechnology are provided in Table 5.

Table 5. Estimates of World Penetration of Recombinant Products in Agri-food

Product	1995	2000	2005	Penetration by 2005
		(US$ millions)		
Veterinary drugs	100	700	2 000	> 10%
Veterinary vaccines	50	500	3 000	50%
Veterinary diagnostics	100	200	300	100%
Animal breeding stock	—	—	20	very small
Drugs from transgenic animals	—	—	?	not yet proven
Microbial pesticides	5	10	100	< 1%
Microbial inoculants	—	5	20	fraction of small market
Transgenic seed	10	700	2 000	substantial
Transgenic produce	15	100	500	5–10%
Horticulture	—	5	10	niche products, very small
Plant diagnostics	100	200	500	100%
Animal feed	20	100	500	10% of total feed additives
Chemicals from transgenic plants	—	20	100	unknown
Total	**400**	**2 540**	**9 050**	

Source: Decision Resources, Biotechnology in Agriculture, September 1995.

Canadian export opportunities are most promising in the short term for canola and potatoes. Canola genetically engineered for herbicide tolerance and superior oil qualities will be available for export in 1996–97 and is expected to capture a share of Canada's billion-dollar export market of the conventional variety. Potatoes are Canada's most valuable vegetable crop, with a farm gate value of over $500 million; 70 percent are exported. Genetically engineered potatoes (for insect resistance against the Colorado potato beetle) will also be available for export in 1996–97. Research is under way on developing improved varieties with disease resistance and on others that will absorb less oil when cooked. Over the long term, wheat and barley have the brightest prospects. Except for canola, exports of transgenic seed are insignificant, as international developers of herbicide and insect tolerance have not provided exclusive access to their technology to any one seed company; instead they issue seed growers in the major agricultural markets a licence for their technology incorporating agronomic traits developed for local soil, climate and pest conditions.

Canola, potatoes hold most promising crop export potential in the short term . . .

Canada supplies about 30 percent of dairy cattle genetics to the world, exporting live cattle, embryos and bull semen to 30 countries. South and Central America hold the greatest potential because of the introduction of crossbreeding programs in those regions using Canadian-bred sires for the production of high-yielding dairy herds. The U.K. is another key opportunity as a result of the bovine spongiform encephalopathy (BSE) scare and that government's decision to cull a large number of cattle.

. . . animal products include cattle embryos and semen . . .

Export opportunities in other agri-food markets are likely to be much more limited. Although Canadian exports of live animals exceed $1 billion a year, the development of new commercial breeding stock with improved characteristics such as growth rate and body composition via genetic engineering is not likely for many years because of technical and public safety issues. As well, genetic selection will compete against established techniques such as improvements in animal nutrition, selective breeding, administration of hormones and sale of embryos.

. . . with limited opportunities for other products due to safety issues

One of the successful applications of biotechnology is likely to lead to reductions in production costs per unit of output, such as increased crop yields or improved livestock feed conversion efficiency. The increase in productivity in turn will increase the international competitive position of the Canadian agri-food sector. The downside is that, as in past agricultural innovations, an increase in supply will result in a corresponding pressure on prices. Unless Canadian producers keep pace with their competitors in the adoption of biotechnology, profitability and market share will decline, because late adopters will be faced with lower product prices.

Canadian benefits of ag-bio-tech are expected to emphasize commodity supply productivity as well as new value-added products

Other applications of biotechnology in agriculture could lead to higher value products such as improved oils (lower saturates) with enhanced health benefits or even products with other industrial (non-food) uses such as pharmaceuticals. These latter applications may be more attractive, as they do not face the same ceiling price constraints of traditional commodity crops.

Aquaculture biotech is still very much in formative stage

Aquaculture currently accounts for about 20 percent of worldwide fish harvesting, with Asia representing 85 percent of production, Europe 8 percent and North America 3 percent. China, Japan and Taiwan lead in the greatest dollar value of farmed marine products. For farmed shrimp, Thailand, China, Indonesia (which is overtaking China), Ecuador and India are the world leaders. Norway and Scotland are the major producers of farmed salmon, followed by North America, Chile and Japan. However, the development of second-generation biotechnology pertaining to aquaculture and marine species is still very much in the formative stage. Scientific research on fish pathogens, for example, is still in its infancy compared with that on humans and animals. There is only a limited number of vaccines on the market, largely to combat bacterial infections but none is yet available for viral pathogens. Although many bioactive substances from the marine environment already have been isolated and characterized (for example, the compound manoalide, which is extracted from a Pacific sponge for investigation as a potential anti-inflammatory agent), few pharmaceuticals have yet been commercialized. Many of these compounds are very large complex molecules, making production difficult. In the area of brood stock development, use of conventional and reproductive hormones in feed as well as monosex manipulation are widely utilized to create faster-growing fish. There has been considerable Canadian research on developing transgenic fish, but it will take years for successive generations of salmon to pass on their genes to their offspring and for these genetically engineered species to overcome regulatory obstacles and gain wide consumer acceptance.

Strong growth is expected for bioremediation, with Canadian firms showing strengths in resource processing

The international market for **bioremediation** is estimated at US$400 million and is expected to double by the end of the decade. The U.S. and the EU account for about 55 percent and 35 percent of the market, respectively, with the EU expected to match the U.S. within five years. In North America, bioremediation represents no more than 2 percent of the total remediation market, compared with 8 percent in Europe. Land sales and public complaints, underpinned by the regulatory framework, generate most remediation demand. Canadian firms have a reasonably strong base of experience in soil bioremediation, targeting mainly government agencies, petrochemical plants and petroleum distributors. However, commercial acceptance has been inhibited by the "black box" nature of bioremediation and time frames for achieving desired results, coupled with varying provincial approval standards across Canada. There is a dearth of basic scientific knowledge about organisms. Before bioremediation's commercial potential can be realized, further research is required on new target contaminants, bioprocess engineering and control, selection and characterization of new naturally occurring organisms with improved

degradation capabilities and development of site diagnosis and monitoring systems. Improved predictive and process validation capabilities and access to field demonstration sites would help stimulate wider use of bioremediation. Unlike in other biotechnology sectors, strategic R&D alliances do not play a significant role and, when alliances are formed, they are most frequently short-term and project-specific. The greatest need is to partner with small and medium-sized environmental engineering firms that are lacking in-house biological expertise but are aware of upcoming remediation projects.

Application of biotechnology in the production of **fuels** and bulk **chemicals** is not financially or technically competitive with current methods and the low price of oil. The most successful application has been the production of industrial enzymes through fermentation.

Biotech enzymes find uses in detergents, food and textiles . . .

The world market for industrial enzymes is estimated at US$1.4 billion and is expected to grow by 5 percent a year over the next five years to reach US$1.8 billion by the year 2000. Enzymes are used in a variety of industries: detergents, starch, textiles, brewery and wine, sugar, fats and oils, and pulp and paper. The major applications are detergents (40 percent), food (35 percent) and textiles (14 percent). Currently, about 50 percent of enzymes are produced via genetic engineering, and this percentage is expected to increase. R&D efforts are targeted at improving functional characteristics such as heat resistance and stability in harsh solvents, finding novel applications for the existing range of industrial enzymes and finding new enzymes for new applications. Major producers are multinationals located in Europe and Japan. Novo Nordisk of Denmark is the world's largest supplier, holding about 50 percent of the market. The European Commission has focussed on bio-enzyme R&D to maintain the competitiveness of its industry. The capital costs, R&D, marketing infrastructure and technical sales required to support the global nature of the industry pose extremely high hurdles for any new entrant.

. . . not very economic in mining . . .

Naturally occurring micro-organisms have been used for **mineral leaching** and metal concentration processes such as for gold and uranium but commercial activity has been restricted to low-grade deposits or tailings not amenable to conventional cyanide leaching. As long as metals are plentiful and easily mined, no economic advantage is realized by microbiological mining. Other applications that are more commercially viable include prevention of acid mine drainage and treating mining effluents. Canada has considerable research strengths in biohydrometallurgy and related environmental applications through CANMET but, because of the economic aspects of mineral production, commercial applications are at the early stage of development and implementation.

. . . used to address environmental concerns in pulp and paper

Environmental concerns are causing **pulp and paper** manufacturers to explore the use of enzymes and bacteria as alternatives to conventional chemicals: agrobacterium to reduce the concentration of halo-alcohol by-products in paper treatment polymers, xylanases in biological bleaching of pulp to reduce the use of chlorine, lipases and cellulases to remove inks and toners from recycled paper, and biological prevention of slime formation in paper making machines. However, biotechnology's role in the pulp and paper sector is still limited: enzyme costs are often too high compared with conventional chemicals such as biocides; the relatively small market size for many of the applications does not justify the development and manufacture of unique enzymes; and most importantly there are major problems in transferring inventions to industry due to the conservative nature of the sector and the inability to arrange mill trials.

Most promising application is forest regeneration

Biotechnology is also playing a minimal role in the **forestry** sector because of production economics. In the wood products area, commercial opportunities for an enzyme or bacterium that will inhibit sapstain fungi to prevent staining of lumber are limited because of small market size. The most promising application of biotechnology is in forest regeneration using somatic embryogenesis, as Canadian researchers are among the world leaders in this area. However, because most forest lands are owned by the Crown, there is little commercial incentive for industry to invest in new technology.

4.2 Key Industry Strengths

Canadian human biotech strengths are medicine, vaccines, providing clinical trials . . .

Canada has strengths in certain fields of research such as medical genetics, cancer and cardiovascular disease and particular areas of product development, notably vaccines. In medicine, Canada benefits from research facilities such as the University of Toronto and its affiliated teaching hospitals, the largest medical faculty in North America. On the services side, a related Canadian strength is in providing clinical trials on behalf of Canadian, U.S. and overseas firms to test the safety and effectiveness of new drugs and in performing regulatory work for submissions to the U.S. FDA.

. . . with expertise also in commercial agri-food and horticulture

Canada also has a strong base in agricultural biotechnology as a result of research conducted by the universities of Guelph and Saskatchewan, the National Research Council's Plant Biotechnology Institute and Agriculture and Agri-Food Canada. Competitive strengths are in animal husbandry, micro propagation/tissue culturing and plant breeding, the latter enabling

western Canada in particular to attract a growing number of plant breeders with strong international links. Canada is also a world leader in the development of somatic embryogenesis for propagation of conifers and flowers, aquaculture vaccines and brood stock optimization as well as in the development and production of yeast strains.

4.3 Current and Anticipated Challenges and Issues

Canadian firms are small, with few commercial licences

In Canada, few products have been commercialized, and the majority of firms are small. University research results are commonly licensed cheaply to foreign multinationals, since few domestic companies have the technical and marketing resources to gather market intelligence, fund international patent costs and exploit new technologies.

Financing remains a challenge for early-stage firms

Patient and knowledgeable risk capital is required because of the long time it takes to bring a new technology to market. While capital has become more accessible in recent years, financing remains a challenge for early-stage companies, particularly in areas other than human health.

Domestic skill shortages are not helped by difficult foreign recruitment

Shortages of skilled labour are expected to arise in certain areas such as bioprocess engineering, regulatory affairs and international business development, which could place Canada at a competitive disadvantage. Canada's tax structure and lower wage levels makes foreign recruitment difficult and also encourages an exodus of key Canadians.

Another major challenge is ensuring that Canada's regulatory system is efficient and responsive to the concerns of both producers and consumers and remains competitive and in harmony with other jurisdictions.

Canada has few suppliers, limited capacities in some areas

There is a lack of major domestic suppliers of industrial enzymes or of genetically engineered food ingredients, as well as veterinary vaccines, to take advantage of growing market opportunities.

Canada has limited U.S. FDA-compliant manufacturing facilities for the production of bio-pharmaceuticals, forcing firms to subcontract production in the U.S. or offshore.

Institutional impediments hold back diffusion of certain biotechnologies

In some areas, there may be a need to focus on certain institutional impediments to the use of biotechnology. In forestry, most lands are owned by provincial governments, so companies have little incentive to take advantage of innovations in reforestation. The pulp and paper sector is traditionally conservative and reluctant to arrange mill trials for new technologies such as biological bleaching or prevention of slime formation.

Despite extensive experience in soil bioremediation, this is not strong enough to differentiate Canadian firms from international competitors. There is a lack of landmark demonstration projects to establish performance claims.

Consumers need to be reassured of biotech safety

There is an ongoing need to address consumer questions and concerns about biotechnology, although this is also a global issue.

4.4 Future Opportunities

Cost advantage relative to U.S. attracts investors, especially in aquaculture . . .

Because of its cost advantage relative to the U.S., Canada is well positioned to attract new investment. Some of the most promising opportunities are in aquaculture health. With the rapid growth in seafood farming, there is a potentially strong market for fish vaccines and pool-side diagnostic tests for early detection of fish disease.

. . . higher-yielding, pest-resistant food crops . . .

In plant biotechnology, main applications are for higher-yielding and pest-resistant canola and potatoes, canola and soybean with modified oil properties, wheat with modified gluten and starch for improved processing and malting barley.

. . . forestry . . .

Forest biotechnology can improve productivity by increasing the hardiness of trees, accelerating their growth and protecting them from pests and disease. The potential in the short term is greatest for genetically improved conifer tree propagules, somatic embryogenesis to accelerate the tree breeding cycle and biopesticides.

. . . cattle cross-breeding in Europe and South America . . .

Canada's excellent reputation for producing healthy cattle combined with its superior dairy genetics and embryo transfer technology can be more fully exploited. South and Central American markets hold the greatest potential because of the introduction of crossbreeding programs in

those regions using Canadian-bred sires. There may also be opportunities in Europe as a result of the BSE scare and the U.K. government's decision to cull a large number of cattle.

With regard to bioremediation, the main opportunities outside Canada are in adjoining U.S. states. Eastern Europe represents a large potential market, but competition from the EU will be intense.

. . . and bioremediation opportunities

4.5 The Bottom Line

Canada is not yet a major competitor in biotechnology but has many promising startup/development stage companies with potential in selected niches. There are significant global opportunities but, despite strong academic research and substantial public investment, commercialization has been slow. Most biotechnology firms around the world still have no product sales and are losing money.

Canada holds promise of becoming major competitor in selected niches

Governments and industry face the following major challenges, among others:

- developing regulations that appropriately balance ethical, environmental and consumer concerns against the costs of government regulations
- fostering a strong academic research base and technology transfer mechanisms and the industrial capability to convert research into products
- building a domestic manufacturing capability by ensuring competitive costs and returns (i.e. quantifying production costs relative to those of other countries and making the case for investment)
- improving the diffusion of the technology to other sectors of the economy and determining what factors influence its adoption
- improving coordination of training and strategic planning of human resources requirements and encouraging apprenticeship programs
- addressing the financing issues, especially for early-stage non-health care companies
- attracting investment and alliance partners to support the cost of clinical trials, regulatory approval and international marketing.

These challenges and issues will be further pursued with industry and other stakeholders in the forthcoming *Framework for Action* document with a view to agreeing on an action plan aimed at improving the competitiveness of bio-industries.

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Annex A
GLOSSARY OF TERMS

Aerobic: Living or acting only in the presence of oxygen.

Agrobacteria: Species of soil-borne bacteria that can induce tumors in plants by introducing a ring-shaped segment of DNA — a tumor-inducing plasmid — into plant cells. Genetic engineers use this principle to infect crop plants with genes for pesticide resistance.

Amino acid: The building blocks of proteins. There are 20 common amino acids that can be combined in various combinations to form proteins. The sequence of amino acids in a protein and hence the function are determined by the genetic code.

Amplification: The production of many copies of a gene or chromosomal sequence.

Anaerobic: Living or acting in the absence of oxygen.

Antibodies: Proteins (also called immunoglobulins) produced by the immune system in response to the introduction of foreign molecules called antigens. Antibodies react specifically with these molecules to prevent infection. An antibody is characterized by a structure complementary to the antigen and is thus capable of binding specifically to it to neutralize it.

Antigen: A substance, usually a protein or carbohydrate, that, when introduced in the body, stimulates the production of an antibody that will react specifically against it.

Antisense: Synthetic segments of DNA or RNA (oligonucleotides) designed to mirror specific RNA sequences and block protein production.

Artificial insemination: The deposit of sperm cells in the female reproductive tract by instruments.

Autoimmunity: A condition in which the body mounts an immune response against one of its own organs or tissues, for example, Lupus or rheumatoid arthritis.

***Bacillus thuringiensis*:** A naturally occurring biodegradable bacterium toxic to various insect pests such as caterpillars and beetles. Different strains confer resistance to different insects.

Bacteria: Any type of large single-cell organisms having round, rodlike, spiral or filamentous bodies that are often aggregated into colonies, are enclosed in a cell wall or membrane and lack fully differentiated nuclei. An example is *E. coli*, which is commonly used in genetic engineering for the production of proteins and other biochemicals.

Biofertilizer: Nitrogen-fixing bacteria such as rhizobia or certain fungi based on naturally occurring organisms used as a fertilizer.

Bioinformatics: The storage, retrieval and analysis of genetic data.

Biopesticide: A biological pest control using naturally occurring organisms.

Bio-pharmaceuticals: Pharmacologically active substances derived from or related to gene sequences.

Bioprocess: A process in which living cells or their components are used to produce a product.

Bioremediation: The use of living organisms to reduce or eliminate environmental hazards resulting from the accumulation of toxic chemicals.

Biosensor: A biological molecule such as an enzyme or antibody used in conjunction with a transducer for the detection of substances such as sugars or proteins in body fluids.

Cell: The basic structure of all living organisms.

Cell fusion: The joining of the membrane of two cells, thus creating a single hybrid cell that contains the nuclear matter of parent cells.

Chromosome: A structure in the nucleus of the cell composed of a DNA protein complex that contains the genetic material (genes).

Clone: A group of genetically identical cells or organisms produced asexually from a common ancestor.

Combinatorial chemistry: The rapid synthesis of massive libraries of compounds from combinations of smaller molecular units.

Cultivar: A term denoting certain cultivated plants that are clearly distinguishable from others by one or more characteristics and that, when reproduced, retain those characteristics.

Diagnostic: The determination of the nature or cause of a disease or condition. Immunodiagnostics or immunoassays refer to a specific market segment of the diagnostics market where various techniques are used to determine the levels of antibodies and antigens.

DNA: Deoxyribonucleic acid, substance from which genes are made. DNA molecules are composed of strings of four subunits called nucleotides or bases. Genetic information is specified by the sequence in which the nucleotide subunits occur in the DNA. There are four bases: adenine, cytosine, guanine and thymine. A specific sequence of three bases can be read or translated by a cell into a specific amino acid.

DNA probe (gene probe): A molecule, usually a nucleic acid, that has been labelled with a radioactive isotope, dye or enzyme used to locate a particular nucleotide sequence or gene on a DNA molecule.

Embryo: An unborn offspring at the earliest stage of development between fertilization and formation of internal organs (up to approximately 50 days after conception).

Embryo transfer: The deposit of an embryo in the female reproductive tract by instruments.

Enzymes: A group of multi-purpose yet individually specialized biological proteins produced by living cells. Enzymes mediate and promote the chemical processes of life without themselves being altered or destroyed. Examples are protease, glucoamylase, glucose isomerase and rennin. One type is proficient at cutting DNA at pinpoint locations, making it possible to add or remove genes.

***Escherichia coli*:** A species of bacteria that inhabits the intestinal tract of most vertebrates. Many nonpathogenic strains are used as hosts for recombinant DNA.

Express: Ability of a cell to produce a given product.

Gene: A small portion of a chromosome that contains the hereditary information for a particular trait, determined by specific sequences of DNA.

Gene probe: A section of DNA of known structure or function marked with a radioactive isotope, dye or enzyme so that it can be used to detect the presence of specific sequences of bases in another DNA molecule.

Gene therapy: The replacement of a defective gene in an organism suffering from a genetic disease. Recombinant DNA techniques are used to isolate the functioning gene and insert it into cells.

Genetic code: The DNA sequence of a gene, which can be used to predict the amino acid sequence and thus the functions of a living organism.

Genetic engineering: A technique involving the transfer of specific genes from one organism to another; also called recombinant DNA technology.

Genetics: The passing of the hereditary characteristics from one generation to the next.

Genome: The total genetic information contained in the DNA of an organism.

Genomics: Directed drug design in which disease-related proteins are identified as therapeutic targets via gene sequencing.

Harvard mouse: A transgenically engineered mouse developed at Harvard University and patented in the U.S. in 1988. The mouse was engineered to be unusually susceptible to cancer and was developed for use in the testing of carcinogens and cancer therapies.

Human genome project: A 15-year (1990–2005) international effort to identify, locate and map genes and to sequence the entire human genome, an estimated three billion nucleic acid base pairs and 50 000 to 100 000 genes. Many common diseases such as cancer, diabetes and cardiovascular have a genetic component. As genes are identified, genetic tests to detect mutations in these genes can be developed and potential new drug targets identified. A major focus has been on developing more cost-effective sequencing techniques and data management technology to handle the vast amounts of information being generated. The project's most immediate impact will be on research and diagnostics resulting from advances in automation and miniaturization of sequencing methods.

Hybridization: The production of hybrid plants from genetically dissimilar parents by cross-breeding two different varieties. Hybrid crops do not breed true; that is, they cannot be produced by replanting saved seed but, depending on the plant, are produced by hand-detasseling to prevent self-pollination, chemical agents that cause male sterility, or genetic engineering.

Hybridoma: A new cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody-producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific (e.g. monoclonal) antibodies.

***In vitro*:** In glass, test tube or other laboratory apparatus; that is, outside the body.

***In vivo*:** In the living organism.

Media: A nutrient system for the artificial cultivation of cells or organisms.

Micro injection: A technique used for the insertion of genes from one cell into another, in which highly purified copies of a specific gene of interest are injected. Copies of one specific gene of interest can be injected into a fertilized animal egg, which is then surgically implanted in a female animal's reproductive system.

Monoclonal antibodies: Highly specific, purified antibodies derived from only one clone of cells and recognizing only one antigen.

Nucleic acids: Macromolecules composed of sequences of nucleotides. Each nucleotide is made up of a pentose sugar, phosphoric acid and a nitrogen-containing aromatic base.

***Orphan Drug Act*:** U.S. legislation enacted in 1983 to help motivate companies to develop drugs to treat rare diseases — defined as affecting no more than 200 000 Americans. The law guarantees swifter and more lenient review by the U.S. FDA and market exclusivity for products for a number of years that were ineligible for patents, were off-patent or had little patent term outstanding.

Peptide: A macromolecule composed of 50 amino acids or fewer.

Plasmid: A small circular piece of DNA found in certain bacteria and functioning independently of the bacterial chromosome. Plasmids are the principal vector for inserting genes into micro-organisms.

Protein: A large molecule composed of 50 or more chains of amino acids in a specific order, which is specified via the genetic code. When folded into its natural shape, a protein will have a unique biological activity. Proteins are required for the structure, function and regulation of cells, tissues and organs. Examples are hormones, enzymes and antibodies. There are many kinds of proteins, each having unique functions, and all essential for cell growth.

Rational drug design: Structural analysis of the active sites of enzymes and known drug receptors in order to deduce the shape of new pharmacologically active molecules that will fit these structures.

Ribozymes: Unique RNA strands functioning as enzymes that target and cleave specific messenger RNA molecules in the nucleus to prevent protein production before they can infect a patient.

RNA: Ribonucleic acid; mirror image of DNA used as a template for the production of proteins.

Somatic cells: Cells other than sex and germ cells.

Somatic embryogenesis: The propagation of genetically desirable plant lineages by tissue culture.

Therapeutic: Pertaining to medicine for treating disease.

Tissue culture: *In vitro* growth in a nutrient medium of cells isolated from tissue.

Transcription factor decoys: Oligonucleotides that carry recognition sites for certain DNA or RNA sequences, competing with proteins that bind to DNA or RNA, inhibiting the transcription of certain genes.

Transgenic: A plant, animal or micro-organism containing one or more foreign gene(s) introduced by genetic engineering.

Triplex: Technology that prevents the expression of a gene to its protein by the insertion of a third strand of DNA into the target gene to prevent the initial formation of messenger RNA.

Vaccine: A suspension of killed or weakened bacteria or viruses, or portions thereof, such as DNA plasmids injected to produce active immunity.

Virus: Any of a large group of submicroscopic agents infecting plants, animals and bacteria and unable to reproduce outside the tissue of the host. To replicate, it must invade another cell and use parts of that cell's reproductive system.

Annex B
GLOBAL PRODUCT MARKETS AND DRIVING FORCES

Human Therapeutics and Vaccines

Both established pharmaceutical companies and dedicated biotechnology firms use biotechnology in their development efforts:

- as a research tool to study the molecular and cellular basis of disease
- in the rational design of new drugs that respond to a particular disease process
- as a production technology to manufacture products that either are not available at all or are not available in sufficient quantity or purity.

Unlike in the 1980s, most emerging biotechnology companies now realize they do not have the necessary resources to become fully integrated pharmaceutical businesses. Instead, to make themselves more valuable as strategic partners, they plan to focus either on a specific technology like drug delivery, rational drug design or gene therapy or on a particular product like growth factors.

Worldwide sales of bio-pharmaceuticals totalled US$10 billion in 1995 in a global market for ethical pharmaceuticals worth about US$195 billion. This represents a market penetration of about 5 percent. The bio-pharmaceutical market is expected to grow to US$16 billion by 2005. Currently, fewer than 20 biotechnology-based drugs are on the market, of which six account for 80 percent of sales (erythropoietin, granulocyte colony-stimulating factor or GCSF, hepatitis B vaccine, human growth hormone, human insulin and interferon alpha). The U.S. accounts for 43 percent of consumption, followed by western Europe at 28 percent, Japan at 23 percent and the rest of the world at 6 percent. Japan's share has slipped from 32 percent in 1992 and is expected to drop to 18 percent within five years because of pricing pressures and tightening reimbursement rules.

There are about 300 bio-therapeutics in various stages of clinical development with cancer, AIDS and central nervous system disorders being the major categories. The estimated market potential for all products in development is US$30–50 billion, but only a fraction will achieve commercial success. Some analysts contend that conventional drugs, which number in the tens of thousands, and the limited number of biotechnology drugs that are already on the market will likely form the bulk of pharmaceutical sales over the near to medium term.

Growth is expected to slow to 3 percent a year over the rest of the decade, compared with 10 percent a year achieved in the early 1990s, as product markets become saturated and price pressures increase:

- Few new significant blockbuster drug launches are on the immediate horizon.
- Most existing drugs have near total market penetration.
- Small patient populations for most bio-therapeutics relative to drugs such as hypertensives and anti-ulcers mean, in addition to lower overall sales, faster market saturation followed by flat sales growth.
- There is a continuing high failure rate in clinical trials because of the complex pathology of many diseases. Few disease processes involve one dominant protein or gene, and it is not yet possible to identify all proteins or genes responsible for a specific physiological process.
- High prices result in increased price pressures and tightening reimbursement rates from government and private insurance payers worldwide. Most bio-pharmaceuticals are priced at US$5 000–10 000 per year and some are considerably higher, compared with US$800 a year for most traditional, chronic care drugs. Instead of accepting higher prices for new drugs without question, payers such as the health maintenance organizations (HMOs) in the U.S. now are demanding demonstration of comparative value and the net economic benefits of new treatments. Traditional clinical trials with their strict focus on safety and efficacy are no longer adequate, and firms are now incorporating pharmaco-economic research into their clinical trial program.

Diagnostics

The diagnostics industry consists of companies that market instruments and reagents for the analysis of tissue and fluid samples to detect the presence of specific substances that are indicators of a metabolic disorder or disease. *In vitro* diagnostic products are subdivided into test categories such as immunoassays, clinical chemistry, haematology, histology and microbiology. The total market is estimated at around US$17 billion, with North America accounting for 37 percent of sales, western Europe for 35 percent and Japan for 20 percent. Penetration of biotechnology is concentrated mainly in immunoassays, which is estimated at around US$5 billion (excluding equipment). This category covers antigen/antibody tests for infectious diseases, thyroid function and reproductive hormones, drug monitoring, allergies and cardiac and tumor markers. Another segment with a significant second-generation biotechnology component is microbiology, where growth is driven by the introduction of DNA probe tests, which are currently estimated at around US$125 million but could reach US$500 million by 2000.

Principal factors driving immunoassay market growth are conversion from low-priced manual methods to higher-priced automated systems; development of new immunoassays to replace other methods of measurement such as electrophoresis; discovery of new biochemical markers for disease screening/monitoring such as cardiac and bone markers; the trend toward decentralization of testing from the laboratory to the emergency room, critical care unit and patient bedside, which has led to the development of novel biosensor technology; and the recent FDA ruling that Premarket Applications (PMAs) may not be required for tumor markers, which could speed the introduction of some tests. The categories with the greatest potential are infectious diseases, cardiac markers, autoimmunity tests, drugs of abuse tests and tumor markers, which are forecast to have growth rates of about 15 percent a year.

Diagnostic procedures are performed primarily in three different markets: the clinical market, which includes hospitals, private laboratories, blood banks, patient point of care and home testing; the life sciences research market, such as laboratories in pharmaceutical and biotechnology companies, universities and government; and the industrial market for food and water quality assurance programs, animal health testing and agricultural testing. Consequently, the end-user market is fragmented; features include high-volume purchases of a few tests such as blood bank screening, large commercial laboratories with tremendous purchasing power, several hundred large hospitals and thousands of smaller hospitals, and the emerging point-of-care, physician office and home-use markets. Hospital and commercial laboratories currently account for more than 84 percent of the *in vitro* diagnostic market and are expected to maintain this share for the rest of the decade. The physician office segment will experience minimal growth because of the negative impact of the U.S. *Clinical Laboratory Improvement Act*, which requires all sites performing non-exempt tests to comply with proficiency testing and quality control standards. Also, more and more U.S. physicians are joining HMOs and therefore are receiving a fixed salary, which eliminates a financial incentive to perform tests in-house. Broad acceptance of point-of-care diagnostics has been slow because of battles within hospitals among laboratory personnel, clinical departments and nursing staff. The over-the-counter (OTC) market is significantly larger in North America than other parts of the world, with sales growth being driven by blood glucose testing for diabetes management. This market is not recommended for small firms because of competition and the heavy investment required in product promotion and consumer education. In Canada, the only home and OTC diagnostics available to the general public are diabetes self-test products as well as pregnancy, ovulation and cholesterol tests. Only the Canadian Red Cross and selected public health, hospital and private laboratories are licensed to perform tests on infectious diseases such as HIV, hepatitis and syphilis; similar restrictions apply in other countries.

The international diagnostic market and immunoassays in particular are characterized by:

- diminishing technology life spans
- maturing and slow growth of most market segments (during the 1980s, the industry as a whole was expanding at about 15 percent a year because of the underlying growth in health care expenditures)
- shortages of trained laboratory personnel
- cost containment pressures such as tightening reimbursement rules for certain tests and pressure on physicians to order fewer tests
- fierce competition and diminishing product differentiation
- declining prices and low margins
- cyclical capital purchasing
- high R&D and marketing costs
- multinational dominance and increasing concentration (diagnostic instrument manufacturers are dominated by large multinationals such as Abbott, Boehringer Mannheim, Bayer, Dade, Sanofi and Johnson & Johnson, with the top 10 firms holding over 70 percent of the market, there is no significant Canadian production; instruments are normally marketed at less than cost in exchange for long-term reagent contracts)
- consolidation among buyers for greater purchasing leverage
- increasing automation and emergence of multidisciplinary instrumentation
- long delays in U.S. FDA approval of new products.

For small players, *in vitro* diagnostics is an extremely difficult sector in which to thrive. To be successful, a diagnostic assay will need to be novel and cost-effective, clinically relevant, capable of being run by a lower-skilled technician, and reimbursable.

Agri-food

Biotechnology in agri-food is not a replacement for established tools but rather an additional approach to solving agricultural problems. For example, leaner meats can be produced through better animal nutrition, selective breeding, administration of hormones some of which may be produced through biotechnology, or development of transgenic animals. Similarly, plants with improved characteristics can be produced through selective breeding using classical methods of genetic modification (e.g. fertilization of sexually compatible plants or the use of chemicals or radiation to mutate the genetic material), cell culture techniques (e.g. cell fusion in which two sexually incompatible plants are hybridized or somaclonal variation, which involves selecting

plants that have been regenerated from undifferentiated plant cells) or genetic engineering that can introduce foreign genes into a plant. Traditional plant breeding involves making sexual crosses between the same species or wild relatives; it is time-consuming and expensive, taking between seven to 12 years to carry out. Genetic engineering enables plant breeders to transfer genes in a controlled manner and to identify and test novel characteristics in the laboratory rather than having to wait for evidence in the field, thus speeding up the breeding program.

Field Crops and Vegetables

World commercial seed sales are in the $15-billion range and consist of two principal segments: field crops such as grain and oilseeds, and vegetables. The greatest impact will come from herbicide-tolerant crops, insect-resistant crops, fungus- and virus-resistant crops (closest to commercialization are potatoes), new hybridization techniques for the production of pure hybrid seed (several years away), crops with improved end-use properties, modification of fruit and vegetable quality (sweetness, flavour, processing), and specialty chemicals from plants.

Most seed research is still based on traditional selective breeding programs. Recombinant seed products engineered for herbicide tolerance or insect resistance are just reaching the market. The biggest impact within the next five years will be in the U.S. and will involve corn, soybeans, cotton, canola, alfalfa and potatoes. Resistance to fungal, bacterial or viral diseases is being genetically engineered for canola, soybeans, wheat and many vegetable crops.

The major cereal crops — wheat, rice and corn along with barley, oats, sorghum, rye and millets — form the bulk of international agriculture. In Canada, work is focussed on developing herbicide-tolerant wheat and barley, but it will be several years before these are commercially available.

After cereals, oil crops are the second most important source of edible calories. About 75 percent of the world's vegetable oil is obtained from four plant species: soybean (30 percent), palm (17 percent), canola (15 percent) and sunflower (14 percent). To date, canola with modified oil/protein composition is the only example of a transgenic crop with a novel seed-quality trait that has been approved in the U.S. for unrestricted cultivation and commercialization. Oilseed canola derived from conventional plant breeding has a Canadian farm-gate value of almost $2 billion, making it one of Canada's top export cash crops. About 50 percent of production is exported, principally to the U.S. as canola oil and oilmeal for livestock. Europe (seed), Japan (seed, oilmeal) and Mexico (seed) are also significant export markets.

Substantial work has been devoted to developing crops for the production of food ingredients: specialty vegetable oils such as high-oleic/low-linolenic canola and soybean oil (mainly through conventional breeding but genetic engineering promises to add new functionalities) and modified starch crops.

The relative fatty acid composition of oil varies between species but all contain polyunsaturated fatty acids, which are prone to oxidation during storage and chemical changes during cooking, which in turn result in off-flavours. Being liquid at room temperature, they are unsuitable for margarine. Thus most edible vegetable oils used in food applications such as frying, margarines, shortenings and hydrophobic coatings for cookies, crackers and other snack foods use oils that have been modified by chemical hydrogenation after refining. However, hydrogenation results in the formation of trans fatty acids, which are suspected to increase blood cholesterol levels. By using genes that alter the fatty acid profile of vegetable oil plants, hydrogenation can be eliminated. Most of the development work has been conducted in canola and soybeans. Transgenic canola with a modified oil composition was produced commercially in the U.S. in 1995. Research is under way in Canada and the U.S. to produce non-edible oils with modified fatty acids for targeted applications as lubricants, detergents, plasticisers, cosmetics and coatings.

Linseed flax is Canada's fifth largest crop, with an annual production of two million acres (800 000 ha). It is grown mainly for its oil, which is used as an industrial drying oil in paints, varnishes, etc. Research efforts are under way, using either conventional breeding or gene transfer, to modify the fatty acid profile of linseed flax for other more diverse applications such as high-quality edible vegetable oil found in Becel™ margarine and as a cocoa butter substitute.

Despite achievements over the past decade, many growers and industrialists are still concerned about the commercial future of oilseed biotechnology:

- Most of the transgenic canola varieties currently under development are substitution products aimed at existing markets or aimed at displacing another plant oil; for example, lauric rapeseed would displace conventional coconut-derived lauric oils in detergents. The economics of such substitutions is open to debate.
- Increased production of oil crops for industrial uses will involve the accumulation of associated by-products such as glycerine and oil meal. Economics will be dependent on increased demand for these by-products.
- There has been a proliferation in the development of new transgenic canola cultivars, designed for different and often incompatible downstream uses, ranging from pharmaceuticals to lubricants, detergents and margarines. This may cause formidable problems of seed segregation and identity preservation during cultivation, harvesting and crushing, in order to prevent cross contamination.

Among the cereals, the processing quality of wheat is a research priority, as the proportion and structure of the proteins in gluten affect the properties of wheat dough and the quality of leavened bread. In addition, starch, which comprises 60–70 percent of a wheat grain, has recently become a target for wheat improvement in Canada and elsewhere; in the Pacific Rim and South America, wheat is consumed as noodles and flat breads and their processing is affected by starch structure and quantity.

Barley is the fourth largest cereal crop in the world, of which 40 percent is grown in Europe, 25 percent in the former USSR and 13 percent in North America. It was formerly used extensively for human food but its major use today is for livestock feed, in particular for pigs and chicken, and as a malt for beer and whiskey production. Most breeding efforts are directed toward malting barley because of the higher value of this crop. Work centres on resistance to fungal infection, fast germination, low protein content and the level of starch- and protein-degrading enzymes.

Potatoes, which are grown in every province but are particularly important to Prince Edward Island, New Brunswick and Nova Scotia, are Canada's most valuable vegetable crop. Exports are valued at $350 million divided among seed potatoes ($46 million), fresh table stock ($94 million) and processed products such as french fries ($210 million). The U.S. is the major export market, followed by Venezuela and Japan. A portion of this market will be supplied by potatoes genetically engineered for insect resistance against the Colorado potato beetle. However, it may be some time before significant penetration is seen in the fast food market until fast food chains are convinced that potential consumer fears are alleviated.

Specialty Chemicals

Plant and animal systems could potentially be used to produce high-value compounds at low cost. Gene transfer methods are under development in Canada and elsewhere to increase the value of canola by producing novel high-value pharmaceutical proteins and peptides such as the blood anti-coagulant hirudin. Although the plants are relatively inexpensive to cultivate, separation and purification costs may be significant manufacturing barriers.

Biological Pest Control and Fertilizers

Biologically based technologies (BBT) for pest management consist of a number of different technologies:

- Microbial pesticides (formulations of live or killed bacteria, viruses, fungi and other microbes that are applied to suppress pest populations) are produced by more than 20 companies. World

sales total some $125 million, with the U.S. accounting for about 50 percent. The most widely used is *Bacillus thuringiensis* (Bt). Some 250 microbial pesticides are now registered with the U.S. Environmental Protection Agency (EPA), primarily for vegetable crops, with recent increases in use on potatoes, corn and cotton following the development of new Bt strains and delivery methods. Interest by the lawn and landscape industry has been patchy because of inconsistent performance.

- Living organisms can be used as natural pest enemies, for example, insect predators, parasites and pathogens. The world market is $40 million, with the U.S. accounting for $8 million. As many as 130 companies in North America produce or supply natural enemies, with Koppert (Netherlands) and Bunting & Sons (U.K.) dominating production. More than 100 species, primarily insects and mites, are marketed. These living products have a short shelf life, require temperature-controlled handling, are labour intensive and application must be carefully timed to weather and pesticide spray schedules.

- Pheromones are pest behavior-modifying chemicals to trap pests or disrupt mating and thereby reduce successful reproduction. They are produced by some 15 companies in North America, of which only two actually synthesize the chemicals. The world market is estimated at $60 million (60 percent controlled by U.S. firms).

- Genetic manipulation of pests suppresses their reproduction capability.

Although these technologies receive favourable consideration from regulatory authorities (of the 40 pesticides registered by the U.S. EPA in 1995, half were biologicals), they account for only 2 percent of the pest control market in the U.S. and 1 percent internationally. In general, BBT adoption has occurred most frequently where conventional pesticides are unavailable (e.g. because of pest resistance or small market size), unacceptable (e.g. in habitats that are environmentally sensitive), economically not feasible (e.g. because the cost of pesticide use is high relative to the economic value of the crop) or under increased pressure from consumers opposed to their use due to environmental safety issues. Relative to conventional pesticides, many BBTs act slowly, have a narrower target range because they must coincide with a particular vulnerable life stage of the pest or proper weather conditions for application, have a shorter field persistence and shelf life, and suppress but do not actually eliminate pests. Current use of BBTs in arable agriculture is confined almost completely to insect pests; they have virtually no role in the control of weeds (except for weeds that block navigational waterways), even though this use accounts for almost 60 percent of conventional pesticides in the U.S. Obstacles to

expanded use of BBTs include lack of application knowledge by many pest control practitioners, lack of cost-effective production and packaging techniques, the intensive use of labour for production of many of them, cosmetic standards such as colour and surface defects in fruit, vegetable and nut crops (which make use of conventional pesticides almost unavoidable for produce intended for export markets), limited effect against only a few pests (whereas chemicals have broad effect), typically minute niche markets that result in low profitability (which cannot support increased research), and their inability to fit easily into the existing system for pesticide distribution, sale and use.

New bio-insecticides based on genetically modified microbial Bt strains have been developed. These are an improvement over the wild strains used for years because they are more potent, they do not have to be applied as often, some have an increased range of target pests, while others target specific pests for which no biopesticide currently exists. However, their usefulness in controlling pests is limited by the length of time it takes to kill their insect host and their potential effect on non-target species, especially beneficial insect predators. The development of suitable formulations and application strategies so that the biocontrol agent survives under field conditions is another major stumbling block. Also, the availability of insect, fungus and virus resistant plants will compete against biological agents.

Biofertilizers using nitrogen-fixing bacteria such as rhizobia and some fungi are based on naturally occurring organisms. Recombinant products are not yet commercialized in Canada. Research focus is on genetically improved rhizobia. However, there is little evidence to date that these will be more than incremental improvements over current products. Significant yield increases in the field are difficult to observe and any increase has occurred only at a location where both soil nitrogen content and native rhizobial populations were low. In addition, a wide range of other parameters must be satisfied to enhance nitrogen fixation: moisture, selection of genes chosen to enhance the rhizobia, selection of experimental design and the management/ harvest system used to grow the inoculated crop. Any limitation in one reduces the plant's need for nitrogen or the ability of the engineered strains to form nodules.

The Bulk Feed Industry

Feeds are any substances that provide nutritional requirements to livestock or prevent or correct nutritional disorders. Most feed ingredients are bulk plant commodities. However, these are deficient in essential nutrients. Bulk amino acids, enzymes, hormones, vitamins, antibiotics and other ingredients must be added to the feed ration. The world market for these nutritional feed additives is approximately US$3.3 billion. Most of these products are produced via fermentation, which is expensive and in which Canada has negligible capability. Canada's strengths lie in modifying bulk feed ingredient crops to improve feeding value such as high-oil canola and soybean meal.

The most significant impact of biotechnology on the feed industry is the development of genetically engineered plants with specific feed characteristics and improved feeding value, improved feed enzymes, more efficient production of amino acids and vitamins through genetic engineering and improved detection methods for feed contaminants. The largest U.S. feed manufacturers have little investment in biotechnology for improving feed ingredients. Development efforts will come from seed companies, technology companies and animal health firms.

Digestive enzymes such as phytase are added to cereal grains to improve the availability of phosphorus in poultry and pig diets and to assist in fibre digestibility. Addition of b-glucanase and arabinoxylanase enzymes in cereal-based broiler diets can improve weight gain and food conversion efficiency. However, these enzymes are produced via fermentation and are expensive, which has limited their widespread use. Several countries including Canada are investigating the production of industrial enzymes in starch or oil seed crops, which could then be used as feed meal.

The use of antibiotics and growth promoters is well accepted in improving feed utilization, but the pressure to remove such products from animal feeds is growing. This has already happened in Sweden, Denmark and Finland and may spread throughout the entire EU. Development of recombinant antimicrobial products represents an alternative strategy.

Animal Health

The world animal health market totalled some US$13 billion in 1994, with a real average growth of 6 percent. The key segments are antibiotics, vaccines, medicinal/nutritional feed additives and anthelmintics (antiparasitics). Consumer-oriented, small-animal products were the key contributors to this growth. The industry is served by large multinational pharmaceutical, chemical and biological companies with the top 10 firms (e.g. Pfizer, Ciba Geigy/Sandoz, Merck, Bayer) controlling 56 percent of the market (73 percent in the U.S.). The industry overall exhibits signs of market maturity: slow growth in animal population, excess manufacturing capability, high costs of developing new products, and restructuring of manufacturers and distributors. Biologicals and vaccines, however, will continue to expand as firms focus their R&D investments in preventative products.

The world veterinary vaccines market totals US$1.6 billion. Several genetically engineered vaccines have been commercialized and others are under development including in Canada. These deliver improved performance without the risk of disease, mortality, stress or productivity degradation associated with traditional vaccines. Attempts to develop antiparasitic vaccines have met with numerous failures, with the exception of a recombinant vaccine for a parasitic helminth of sheep.

Animal Breeding Stock

Attempts to apply genetic engineering to breeding have generally been disappointing. The work has usually focussed on applications in aquaculture (fish are especially suitable for transgenic study because most species generate a large number of eggs that are fertilized externally), use of animals to produce high-value chemicals in milk, and improved breeding stock of livestock and poultry. Another goal in animal breeding is the commercial separation of spermatozoa to allow selection of the sex of the offspring; this is of great economic potential for the dairy industry, where females are the income producers. Also, as in plants, genetic marker analysis is being employed in cattle and sheep to detect the chromosomal regions contributing to genetic inheritance traits such as growth rates and fat content.

The transfer of foreign genes into animals has been demonstrated in a number of species: extra copies of growth hormone gene in mice and fish, transfer of genes coding for the synthesis of sulfur containing amino acids to sheep to improve wool growth, genes for resistance to flystrike in sheep and genes for the expression of pharmaceutical proteins in the milk of sheep, goats and cattle. However, the control of growth and body composition is complex, with considerable variation of results in animal species. The site of integration of genes cannot be controlled with current methods, and these applications must meet acceptable standards of animal welfare as well as environmental and public safety before they are commercially available.

Genetic selection through advances in semen collection, cryopreservation and artificial insemination have already transformed breeding programs, particularly in the dairy and beef industry, resulting in improved milk and meat production and traits such as growth rate and carcass quality. In other species, these have limited use because of technical difficulties. Embryo transfer is a relatively new field compared with artificial insemination but is now routinely used on elite cows of most breeds. More recently, requirements for large numbers of embryos coupled with advances in molecular biology have led to the development of *in vitro* fertilization techniques, which has reduced the cost of embryo production and makes it possible to produce clones of identical animals.

Diagnostics

Rapid testing kits are used internally by food processors, animal and crop protection companies as well as government inspection programs and contract laboratories for detection of toxins, detection of pesticide residues or animal drugs in agricultural products, detection of pesticides in the environment, diagnosis of animal diseases and plant disease organisms, and detection

of microbiological contamination of foods and agricultural products such as *E. coli* and *Salmonella*. Increasing stringent government regulations for the detection of pathogens in meat, poultry and fish will stimulate growth. However, this is a crowded sector served by over 20 firms, with low barriers to entry.

Aquaculture and Marine Biotechnology

The global aquaculture (fish farming) industry including aquatic plants is estimated to be in excess of US$25 billion. Potential applications of biotechnology in aquaculture include:

- diagnosis and treatment of infectious disease for increased yields
- brood stock optimization to produce fish stocks with increased growth rates, better disease resistance and improved feed conversion ratios, using techniques ranging from sex selection and polyploidism to DNA modification
- bio-engineered micro algae for cleanup of toxic wastes
- production of bio-active and valuable industrial compounds from marine organisms such as food colourings, polyunsaturated fatty acids for food supplements and naturally derived therapeutics.

However, the application of second-generation biotechnology to aquaculture is still very much unexplored territory. Only a few specialized facilities, located mostly in Japan and the U.S., are dedicated to research in aquatic biotechnology, but in the U.S. less than 2 percent of total federal government investment in biotechnology is devoted to marine applications.

Pharmaceuticals

Marine environments harbour a wide diversity of animals and plants with metabolisms that produce diverse bioactive products. However, the vast majority of marine organisms have yet to be identified and few bioactive compounds have been commercially produced from micro algae or fish species. Although many bioactive substances have been isolated and screened, the molecules are usually very large and complex, making traditional chemical synthesis difficult. A more effective approach may involve transferring the genes of interest into a non-marine micro-organism such as *E. coli* for production through fermentation.

Environmental Cleanup

Marine algae, bacteria and by-products from marine organisms have the potential for detoxifying various contaminants; micro algae have a particularly high affinity for metal. However, there is only one known bioremoval product on the market in the U.S. derived from the algae

Chlorella and *Spirulina*. Most biosorptive systems are laboratory-based and have not been assessed under real operating conditions. Genetic modification to produce strains with higher binding capacity could lower costs.

Diagnosis and Treatment of Infectious Disease

At least 50 different diseases affect aquatic animals, with at least 10 percent of cultured fish lost to disease. This is expected to increase as a result of the trend toward higher stocking densities. Diseases may be caused by polluted water, contaminants in feed, and various viruses, fungi, bacteria and parasites. Disease outbreaks often occur when poor conditions causing stress are combined with the presence of opportunistic pathogens. Stress may be caused by physical damage to the organism, crowding, handling and poor water quality conditions such as widely fluctuating water temperatures, low dissolved oxygen levels and high ammonia concentrations. Disease prevention is accomplished by good husbandry practices such as maintaining proper environmental conditions, good sanitation and nutrition, breeding disease-resistant varieties, using disease-free stocks, reducing stress, using chemical treatment such as hydrogen peroxide or sodium hypochlorite to eliminate fungi, vaccinating organisms, and rapidly diagnosing, isolating and treating disease outbreaks.

The aquaculture health segment is valued at approximately $140 million, consisting mainly of nutritional feed substitutes and conventional antibiotics. The development of drugs and vaccines has not kept pace with the growth in farmed seafood because of the lack of scientific knowledge about fish pathogens, difficulties in administering vaccines to farmed populations, an expensive regulatory approval process (as drugs can be approved only on a species-by-species basis for a specific application, which discourages product development for non-native species) and the limited size of the North American market relative to agriculture or human health care. Compared with other animal species, fish vaccines are not widely used in the U.S. or elsewhere, because they are costly, are available for only a narrow range of cultured organisms and provide protection against only one type of disease. Consequently, only a handful of drugs, vaccines and antibiotics have been approved for aquaculture use. For example, of the 15 vaccines licensed with the U.S. Department of Agriculture, 12 are used specifically for salmonid production, one can be used for catfish, and two can be used for any finfish. This has resulted in a minuscule global vaccine market of some US$6 million, principally for trout and salmon. Europe and the U.S. are the major outlets, as farmers in the developed countries are usually better educated and have the resources to purchase vaccination programs. Market penetration in developing nations has been limited because of a lack of comprehensive marketing, distribution and training programs. However, based on the tonnage of fish harvested and incidence of disease in these countries, market opportunity is estimated at around US$100 million. Of this, shrimp vaccines hold the greatest potential in Asia and Latin America, with an estimated annual market of US$85 million.

A considerable amount of work in developing diagnostic tests for early detection of disease is under way. Early detection of fish disease is vital because there are few vaccines for prevention of major outbreaks. The world market for diagnostic tests is currently estimated at $33 million. Most diagnosis is currently based on cell culture techniques in laboratories and universities away from fish farming operations and is time consuming and expensive. Few pool-side test kits are commercially available and therefore represent a significant business opportunity. Success is dependent on increased genetic information on pathogens, improved purification of such pathogens for analysis, improvements in sample treatments and availability of specific monoclonal antibodies. Also under development are kits for the detection of toxins and pathogens in seafood which can rapidly and accurately assess the safety of seafood for human consumption.

Genetic Improvement

Fish are generally well suited to biotechnological manipulation compared with other animal species because of their short life span, large number of offspring and external fertilization. Triploidy (a process that inserts an extra set of chromosomes into the egg to create a sterile species) and monosex manipulation are used to create faster-growing fish that would not waste their growth strength on egg production. The administration of conventional growth and reproductive hormones via feed is also widely utilized.

Transgenic fish have been produced since 1985 through micro-injection and electroporation. Existing work focusses on transferring genes for growth hormone function and enhanced disease resistance involving mainly coho and Atlantic salmon and channel catfish, as well as other species such as striped bass, tilapia, rainbow trout, gilthead sea bream and common carp. Similar activity is being conducted in shellfish because accelerated growth would prove a boon for culture of slow-growing mollusks as well as sport fishes such as northern pike, walleye and largemouth bass. Transfer of antifreeze protein genes (from fish that live in icy waters such as wolf fish, sea raven or winter flounder) into economically important species such as salmon would promote the development of sea-pen aquaculture in colder climates. In the ornamental fish sector, developments are under way to produce fish with unique colours or patterns. However, technical issues to be resolved include the likelihood that the gene of interest will be inherited in successive generations and the viability of the offspring. In the area of disease resistance, gene transfer has been posed as an option for reducing losses, but suitable candidate genes have not yet been identified. A decade of Canadian research in this area has attracted international interest but it will take about 10 years for successive generations of salmon to integrate the genes into their offspring. Producers of such animals must overcome serious consumer scepticism and regulatory obstacles before the technology is commercialized.

Environment

Environmental biotechnology is not a new field: composting and wastewater treatment are examples of "old" biotechnologies. Biological approaches in the treatment of municipal and industrial wastewater have been well established for many years and the market is mature due to the large base of installed facilities. These systems rely on aerobic bacteria to convert many organic compounds into less toxic species and use a variety of aeration devices to supply the oxygen required to sustain the metabolic activity of the biomass. The major limitation for industrial applications is the wide variability in removal efficiencies resulting from changes in effluent concentration.

Bioremediation of hazardous wastes is the most rapidly growing market segment because of numerous opportunities (estimates for cleaning up U.S. federal government lands alone may be US$450 billion), public acceptability, comparatively low cost, minimal site disruption and benign environmental impact over more conventional waste treatment technologies such as incineration. However, it is not always the technology of choice because of the time required to degrade the contaminants and because efficacy and rate of degradation at any particular site cannot be predicted reliably.

Current commercial applications of bioremediation rely on the use of multiple strains of naturally occurring organisms to reduce or eliminate environmental hazards in soil and water. The use of plants to concentrate pollutants (phytoremediation) is an emerging research area. The use of genetic engineering to develop organisms with special capabilities for waste degradation has been limited because of public perception and regulatory concerns about their effect on ecosystems. The vast majority of contaminants treated to date are petroleum derivatives and fuels, solvents such as acetones and ketones, and polyaromatic hydrocarbons found in coal tars and creosotes. Some chemicals such as chlorinated solvents, polychlorinated biphenyls and high molecular weight polyaromatic hydrocarbons are more resistant to microbes.

At present, biological methods make up no more than 1–2 percent of the total North American hazardous waste remediation market, a share that will increase only gradually, whereas in Europe, particularly in the Nordic countries, bioremediation accounts for a much higher market share of about 8 percent. The present world market for bioremediation is estimated at US$300–500 million, with the U.S. accounting for about 55 percent, western Europe 35 percent and Canada 7 percent. Services account for about 75 percent of cleanup expenses and purchased products (micro-organisms, nutrients, stimulants, equipment, etc.) for 25 percent. The U.S. market is driven by the EPA's efforts to promote innovative technologies, spending on

underground gasoline storage tank cleanup and federal government spending at sites owned by the departments of Defense and Energy. The principal activity in Europe is in the Netherlands, U.K., Nordic countries and Germany, as these markets have progressive policies toward hazardous waste cleanup. Japan has been relatively inactive in bioremediation research. Eastern Europe represents a very large potential market that will open up as its economies recover; however, competition from the EU will be intense. Although some opportunities exist in Latin America, its environmental needs differ as these countries are building their environmental infrastructure from a very low base and have allocated their limited resources to basic water supply and treatment ahead of cleaning up contaminated sites. U.S. opportunities in adjoining states are more feasible.

Cleanup projects typically involve five phases: site assessment to identify the geologic parameters, identification of the hazardous substance, characterization of the site to determine the extent of the contamination, specific plan of treatment, and monitoring. The biological and physical complexity of the field environment requires a multidisciplinary research team composed of microbiologists, ecologists, engineers, hydrologists, geochemists and other specialists.

The market is served by:

- diversified national and regional consulting engineering firms that offer expertise in many different treatment technologies
- dedicated bioremediation service providers
- microbial culture manufacturers who market prepackaged cultures of specially selected organisms
- bioreactor manufacturers
- suppliers of nutrients
- environmental testing companies
- firms that have developed proprietary expertise to address their own internal waste problems.

Because bioremediation is one of several treatment options, the market trend is toward engaging diversified engineering consulting firms that offer full service capability and have the expertise to deal not only with clients but also with regulatory agencies, lawyers, insurance companies and lending institutions.

Annex C
REGULATORY POLICIES

Biologicals/Bio-pharmaceuticals

The problems facing bio-therapeutics are different from those of conventional drugs. About half of the bio-pharmaceuticals in late-stage development (Phase III) have failed to achieve approval. Many product setbacks for bio-therapeutics have been linked to inadequately designed clinical studies, failure to identify patient groups for which efficacy could definitely be established and failure to establish their criteria or end points. Many studies are for indications and diseases for which there have been no previous controlled clinical studies, so there are no road maps to outline the indications, the types of protocols that might be used or the types of problems that may occur. Many of the diseases targeted are not being adequately treated at present, so there is often no general agreement on how best to design or determine such aspects of clinical trials as the appropriate clinical end points or the time frame over which mortality end points are determined. Clinical trials traditionally measured the effectiveness of a potential new drug by determining its impact on clinical outcomes such as death, length of survival or disease progression. However, trials based on clinical end points may require a long time to complete as well as large patient populations.

Review by the U.S. Food and Drug Administration is rigorous and demanding, requiring demonstration of clinical efficacy. Many other jurisdictions, however, accept non-clinical or surrogate markers that are indirect indicators of changes in health. Moreover, the FDA requires two separate studies demonstrating statistically significant efficacy using different patient populations or different clinical end points, whereas a single study may be used elsewhere. The FDA has permitted drug sponsors to include data from clinical trials conducted in other countries but there must be at least one U.S. trial in order to validate the foreign data. This is because of the FDA's concerns about preferred trial designs between the U.S. and other countries, a general lack of adherence to clinical protocols among foreign investigators, difficulty in reviewing and verifying foreign clinical records, and differences in population characteristics, diagnostic procedures and therapeutic practices that may affect the pharmacological potential of the drug. Japan has been reluctant to accept foreign clinical data because of differences in diet, race and climate. On the other hand, it has relatively loose efficacy requirements, which has limited the acceptability of Japanese clinical results in other countries.

The FDA recently has implemented procedures for accelerated approval of all new drugs for life-threatening illnesses in certain circumstances. The new procedures are invoked when studies show promising signs of usefulness, based on analyses of surrogate markers whose fluctuations are indicative of disease progression, such as CD4 T-cell counts (an indicator of the strength of

a person's immune system and thus the progression of human immuno-deficiency virus or HIV infection) or HIV viral load tests such as HIV RNA levels in plasma. The difficulty is identifying appropriate markers, when definitive information on safety and efficacy is not yet available. Companies having had a drug approved under accelerated approval regulations are then required to conduct more definitive clinical end-point studies following product launch to confirm the drug's clinical benefit. If the company fails to show due diligence in conducting clinical end-point and post-marketing clinical trials or if these trials fail to demonstrate clinical benefit, such as incidence of opportunistic infection and survival, to the FDA's satisfaction, the FDA may withdraw its approval.

There have also been recent significant improvements in FDA approval for bio-pharmaceuticals. Previously, companies were required to identify an approved manufacturing plant and apply for an establishment licence for that site specifically, before approval of their product, thus increasing financial risk if the product was not approved. Another requirement included the inspection of every lot before release. In December 1995, the FDA announced that the Establishment Licensing and Lot by Lot Requirements would be repealed for "well-characterized" biotechnology-derived drugs. In March 1996, the FDA adopted new rules to further reduce approval hurdles for certain anticancer drugs. These drugs may be eligible for accelerated market approval if they are shown to shrink tumor size, even if the shrinkage is temporary, and companies no longer have to demonstrate either increased long-term survival rates or improved quality of life.

Europe has had a better reputation for the efficient approval of health care products than the U.S. FDA, making that area of the world often the first point of market entry. The recent establishment of the European Agency for the Evaluation of Medicinal Products (EMEA) in London as the central decision body to provide an approval process that covers 15 national markets is expected to improve on this efficiency. The first bio-pharmaceuticals to go through the EMEA process — Serono's infertility treatment, Schering's beta interferon for treating multiple sclerosis and Rhône Poulenc Rorer's anticancer therapy Taxotere — were approved within one year of startup of the new agency.

There is some debate about the relative speed of the European and U.S. drug approval process. Although anecdotal comments suggest the FDA is slow, the U.S. General Accounting Office states that review times have shrunk considerably from 33 months in 1987 to 24 months in 1994, but are still significantly longer than the recent EMEA approvals. However, the FDA contends most comparisons are not valid: when the FDA grants approval, a company can immediately start marketing its product, whereas in Europe the company must then proceed to conclude pricing negotiations with the relevant authorities in the individual member states before marketing can take place. A notable FDA success story is Genentech's Pulmozyme, in which a joint review and coordinated decision process were undertaken with the Canadian Bureau of Biologics.

This product, a treatment for patients with cystic fibrosis, received marketing approval from the Health Protection Branch and the U.S. FDA in only nine months after submission of the Product Licensing Application and five and a half years after initial cloning of the gene that directs synthesis of the enzyme. The key to success was the early interaction of company scientists with cystic fibrosis specialists and with the regulatory authorities in both countries to identify clinical strategies and data requirements as the basis of trial design, plus the incorporation of quality-of-life and pharmaco-economic measures in the studies. Such meetings are now perceived as the basis for setting protocols, which, if successfully followed, should lead to approval.

Medical Devices/Diagnostics

Approval times for medical devices/diagnostics are up to three times longer in the U.S.: over 700 days compared with 80–120 days in Europe, provided that the manufacturer has passed an EU facility inspection. *In vitro* diagnostics have essentially been unregulated outside North America because the onus is on the market to validate their value, whereas U.S. authorities require proof that the tests do certain things accurately and consistently. The FDA requires clinical trial data for all novel diagnostics but, in Canada and most European countries, the manufacturer currently needs only notification of marketing. New, lower-risk devices have entered the EU with no delay once a manufacturer has passed the initial facility inspection, while similar products take about six months to get approval in the U.S. In addition, diagnostics sold in the U.S. must comply with U.S. current good manufacturing practice (cGMP) regulations, but at present there are no similar restrictions in other countries, including Canada.

In Canada, *in vitro* diagnostic (IVD) products will be subject to new regulations utilizing risk-based classification, which come into force in April 1998. Classes III and IV will require submission of clinical data to satisfy the premarket approval process (PMA). At the present time, IVDs are subject to notification only, except HIV test kits. Good manufacturing practice (GMP) requirements are scheduled to be implemented by year 2001.

In the U.S., there are three risk classes of medical devices — I, II and III. New devices enter the market in one of two ways: through a premarket notification process authorized under section 510(k) of the U.S. *Federal Food, Drug and Cosmetic Act*; and through a more extensive premarket approval application (PMA).

Under the 510(k) process, the FDA must determine whether a device is "substantially equivalent" to a device that is already legally marketed. A manufacturer using the premarket notification process informs the FDA about the device and why any changes in its device can be made safely. (Some low-risk devices have been exempted from premarket notification.) If the FDA finds the device to be "substantially equivalent," the manufacturer may market the device and must then

comply with GMP requirements to ensure that the device is properly made. More than 90 percent of all devices enter the market under the premarket notification process. The more extensive PMA is targeted toward Class III devices.

Diagnostic products sold in the U.S. for research use only do not require FDA approval prior to marketing, but must be properly labelled as such. The FDA has begun to impose new distribution requirements and procedures on companies selling research-only products, including that the seller receive specified certifications from its customers about their intended use for it.

Until recently, U.S.-manufactured medical products that had not received U.S. FDA approval for sale in the U.S. could not be sold abroad, even if the product had received marketing approval in the country for which it was destined. This provided a strong incentive for these firms to establish production facilities as well as their clinical trials and research activities overseas. The Irish and Netherlands governments, for example, highlighted FDA regulatory delays to attract U.S. businesses. However, an amendment attached to the budget bill recently signed by President Clinton states that these products can be exported anywhere in the world, provided that they have received marketing approval from regulatory authorities in the EU or any one of seven countries who have reviewing procedures that are internationally recognized as competent: Canada, Japan, Australia, Israel, Switzerland, South Africa and New Zealand. Implementation of this amendment depends on how the FDA interprets some of the more complex provisions and how diligently it chooses to administer it.

The EU regulatory framework requires a product to conform to the essential requirements laid down by a relevant directive. The method of demonstrating conformity varies from directive to directive and from product class to product class, but normally involves a combination of:

- manufacturer's self-certification
- third-party audit of the manufacturer's quality system and
- third-party testing of the product.

The EU system is based on the ISO 9000 series of standards (Quality Management), in Europe designated as EN29000 series and EN45000 series (testing laboratories and certification bodies), under which a facility can be certified by the third party "Notified Body" to the effect the facility/ company meets the standards' requirements for Quality Management. The underlying principle is that if a company has all the necessary function, checks and balances in place, the end products will be reliable and meet the quality expectations.

At present, the EU requirements for *in vitro* diagnostics vary among member states. The new *In Vitro* Diagnostics Directive (IVDD) is in the final stages of development and is based on a risk classification schema. Final adoption was delayed because of difficulties to achieve a common position and is expected by the end of 1997, with a one-year period for national implementation and a two-year transition period. Definitions and essential requirements need some further refinements.

A mandate to CEN/CENELEC (Comité européen de normalisation/Comité européen de normalisation électronique) (standards writing committees) is under preparation for the development of harmonized European Standards on performance evaluation, traceability of reference materials, sterility/microbiological status, stability testing, labelling, IVDs for self-testing/glucometers, devices for blood grouping, HIV markers, rubella, toxoplasmosis markers, etc.

Some changes are anticipated with the implementation of new European directives on product registration. Several elements of the regulations, such as whether all reagents, packaging and instructions are to be printed in the language of the country where the product is used, will present difficulty to manufacturers. Other countries (Australia, Japan, South Africa and China) have indicated they will base their regulation procedures on the European system.

Agri-food

The U.S. has less restrictive regulatory hurdles regarding field trials or to the introduction of ag-bio-tech products. Three separate government agencies regulate the development and commercialization of genetically engineered agricultural and food products: the Department of Agriculture (USDA) for field trials, the Environmental Protection Agency (EPA) for microbial pesticides and genetically pest-resistant plants, and the FDA to determine the safety of food and food additives. The FDA regulates products on the basis of their characteristics rather than on the process used, and therefore does not concern itself with whether the product is produced via genetic engineering or not. However, a food that contains a new protein could be subject to regulation as a new food additive. This is of particular concern for any new food that contains a gene product with reasonable potential for causing allergic reactions such as those derived from peanuts or strawberries. The USDA's regulatory rules extend to the importation, interstate commerce and environmental release of any organism that poses a potential threat to U.S. agriculture. For many genetically engineered crops, these activities require a simple notification. To commercialize a crop that falls under the USDA's rules, the crop must be exempted from further regulation by a formal petition process.

Examples of transgenic crops that have received FDA approval at time of writing include: Asgrow's virus-resistant squash; Calgene's delayed-ripening tomato and bromoxynil-tolerant cotton;

Monsanto's delayed-ripening tomato, insect-resistant potato and herbicide-tolerant soybean; DNA Plant Technology's delayed-ripening tomato; Zeneca's delayed-softening tomato; and Ciba's insect-resistant corn.

The EPA has designated as plant pesticides certain novel pesticidal substances genetically introduced into plants for the purpose of protecting against pests and disease, along with the genetic material necessary to produce the substance. It plans to focus its attention on those plant pesticides posing new exposures and greatest potential for adverse effects. Exempted from the regulations under the U.S. *Federal Insecticide, Fungicide and Rodenticide Act* are those plant pesticides that have been derived from a closely related plant, those that would not result in adverse effects to non-target organisms because they are primarily affecting the plant and coat proteins from plant viruses when produced in plants for virus coat protein mediated resistance. Under the U.S. *Federal Food, Drug and Cosmetic Act*, which governs pesticide tolerance in food, similar exemptions apply. The regulations also contain general guidance on labelling, which would be comparable with those for conventional pesticides; for example, packaging for a bag of seeds would inform farmers of the type of pesticides that the plant will produce and against which pests it is active. With respect to field trials, developers would be required to obtain an Experimental Use Permit before testing on a site greater than 10 acres (4 ha) or greater than a cumulative 50 acres (20 ha) for multiple-site tests.

The problem of insect resistance to pesticides is a worldwide concern. Until recently, the U.S. EPA has not mandated pesticide resistance criteria in its registration process but has worked with companies that have voluntarily submitted a pest management resistance strategy to develop appropriate labels advising users on ways to avoid or delay the onset of resistance. However, in May 1995, NewLeaf Russett Burbank potatoes became the first genetically modified insect-resistant crop to receive full regulatory approval. During the review, unlike in reviews of previous microbial or chemical insecticides, the EPA considered the risk of insect resistance as part of its regulatory assessment. It also required those firms marketing Bt-producing cotton to ensure that non-Bt cotton is planted as a refuge. (The theory is that insects developing resistance to Bt will mate with Bt-susceptible insects coming from nearby non-Bt plants, generating offspring that are less resistant to Bt.) For this strategy to work, it is important that the refugia are large enough and in the right places and that the cotton expresses Bt at high enough levels to kill both susceptible and less resistant insects.

The Canadian regulatory system is comparable with that in the U.S. in most areas, with few real differences. The main differences affect:

- naturally occurring biofertilizers and biofeeds, which are regulated at the federal level in Canada but at the state level in the U.S.

- transgenic plants with pesticidal characteristics, which are regulated as plants under the *Seeds Act* in Canada but under the *Federal Insecticide, Fungicide and Rodenticide Act* in the U.S.; the requirements for registration are virtually the same
- the speed of registration for veterinary biologics, biological pesticides and microbial supplements, which has been generally slower in Canada, but the gap has narrowed.

The regulatory situation in Europe for agri-food products, relative to health care approvals, is complicated and in a state of flux. Currently, any regulatory changes have to be agreed by the Commission, the EU Council of Ministers and the European Parliament, a lengthy procedure. A further problem is that the same legislative requirements — Directive 90/220EEC concerning the deliberate release of genetically modified organisms into the environment — are interpreted differently by EU member states. Directive 90/220 has been identified as a significant barrier to the approval of genetically modified agri-food products and is currently under review. Whereas the U.S. regulatory process is generally focussed on products, these directives are focussed on the process. An indication of the greater difficulties in the regulatory environment in the EU is the disparity in the number of field releases: over 500 in the EU between 1992 and 1995, about the same number as in Canada in 1995 alone.

A genetically engineered product must go through several poorly defined steps on its way to commercialization. The first step in the approval process is to secure permission for field trials from the appropriate country but the willingness varies (France, Belgium and the U.K. are relatively open while Germany is much more resistant). Permits are required from all countries in which trials are to take place, rather than getting one EU-wide centralized permit. The developer then must obtain permits for enlarging the trials and preparing the crop for marketing. At this stage, the dossier is handed for assessment to a member state, where it will first be assessed; the approach involves obtaining approval in one member state and then gaining EU-wide approval. That first country's recommendation is then subject to approval from all member states. EU countries can raise objections to granting blanket EU marketing approval. Finally, the new seeds must go through the normal seed registration procedures for each individual country in which they are to be sold.

Europe gave the world's first marketing clearance to a genetically modified crop when it approved tobacco plants modified to tolerate the herbicide bromoxynil. However, only one of these products has yet reached the marketplace — a tomato paste based on a modified tomato developed by Zeneca, which is now on sale in British supermarkets. Britain has been at the forefront in getting genetically modified seeds through the pan-European approval process and in streamlining regulatory requirements for field trials.

In Japan, experiments and field trials involving recombinant organisms are regulated by several agencies: the Ministry of Education, Science and Culture (research in academia), the Science and Technology Agency (research in institutes and private sector), the Ministry of Agriculture, Forestry and Fisheries, the Ministry of Health or the Ministry of International Trade and Industry, depending on the product category. Food products are under the jurisdiction of the Ministry of Health. Requirements for field tests are stricter than in other jurisdictions, and only six trials have been approved to date. Guidelines for the regulation of recombinant food products are still under development. In September 1994, importation of rennet from genetically engineered organisms was approved. Other imported products are under consideration (e.g. recombinant oilseed canola).

The question of whether genetically engineered foods should be labelled as such has been controversial around the world. The EU and the European Parliament had recently agreed that labelling will be needed only on foods that contain "live" genetically engineered cells. Foods without "live" cells will also be labelled if they differ from conventional foods beyond "accepted limits of natural variation" or if they cause specific nutritional or ethical concerns for consumers, such as potential for allergies. Many consumers were dissatisfied because the regulations are open to interpretation, with few safety guarantees. The issue is still undecided in Japan. However, as a result of the "mad cow" crisis, the European Commission recently adopted proposals that genetically engineered seeds will have to be labelled as such. The new rules do not apply to crops already approved for EU sale, products awaiting approval or on the resulting crops or foods but, by forcing producers to label the original seed, it will enable users down the food chain to identify the source. The Commission planned to update the current directive on genetically modified foodstuffs by mid-1997 and produce a framework document on EU policy for every stage of the food supply chain from farm to consumer. If the FDA reverses itself on the labelling question, these products may have greater difficulty gaining consumer acceptance. Further, the added cost and handling complexity of segregating biotech foods during distribution and processing would make it more difficult for such products to achieve significant market share.

Bioremediation

Canada is different from the U.S. or European countries in that it requires notification prior to import or "manufacture" of naturally occurring micro-organisms (specifically, those not already in commercial use in Canada during the period January 1, 1984 to December 31, 1986). Also, Canada has been divided into a number of ecozones, while the continental U.S. is considered as one ecozone. These two factors may increase the cost of carrying out bioremediation in Canada using naturally occurring organisms, relative to costs in the U.S. or Europe.

Annex D
PATENT ISSUES

Dominant Patents Controlling Enabling Technologies

Most bio-pharmaceutical products are natural proteins based on the cloning of human genes. Consequently, patent protection has tended to focus on the genes encoding therapeutic proteins, isolated and purified DNA sequences, various vectors to insert such sequences into production cell lines, cell lines modified by the insertion of these sequences and methods of propagating cells. Diagnostic companies focus on the discovery of a new antigen, which is a marker for a specific disease and the development of a monoclonal antibody to detect this antigen or a new DNA/RNA diagnostic methodology, filing patents on specific antigens, enzymes and protein sequences. In agriculture biotechnology, many basic development tools such as antisense or the *Agrobacterium* transformation system are held by others or are subject to complex patent disputes that may take years to resolve in the international arena. For example, antisense technology used to "turn off" genes in products such as controlled-ripening tomatoes and products with novel colours is subject to a legal battle between Enzio Biochem, Calgene and Zeneca. A similar situation is the four-way patent litigation involving the *Agrobacterium* transformation system. Any company needing access to these key technologies to commercialize a product must choose which of the contenders to license from. A company needs to explore intellectual property for possible infringement before investing significant research dollars.

Broad Biotechnology Patents

There is a widespread view in the industry that too many broadly based patents have been issued on basic enabling technology. Broadly based patents are more likely to be challenged if licensing is difficult or expensive, thus raising the possibility of being shut out of markets. Gene Therapy Inc. of the U.S., for example, was granted a sweeping patent covering techniques for all methods of *ex vivo* human gene therapy with human cells that have been genetically engineered *in vitro* to express a therapeutic protein. Because three quarters of gene therapies approved for clinical trials involve *ex vivo* therapies, litigation is expected from competing companies. Other examples include the U.S. patent granted to Agracetus covering genetically engineered cotton, the first patent covering all transgenic forms of a single crop; a broad patent to Agracetus granted by the European Patent Office (EPO) covering genetically engineered soybean; Calgene's patent for *Brassica* transformation granting broad rights to all transformed varieties of this particular crop with a particular trait; Mycogen's broad patent covering any method of modifying *Bacillus thuringiensis* gene sequences for making plants resistant to insects; and patent filings in Europe (and reportedly the U.S.) by Pioneer for transformed

canola. The ability of industry to obtain broad patents in the future is unclear. The House of Lords in the U.K. recently invalidated Biogen's British patent to all recombinant DNA molecules coding for hepatitis B antigens on the basis of being overly broad. However, in most other EU countries, patent decisions are governed by the European Patent Convention (EPC), under which a patent cannot be challenged on the breadth of its claims once it has been issued. Recent attempts by industry to change this rule were unsuccessful. In the U.S., patents can be challenged on the basis they are too broad, and the Commissioner of Patents and Trade-marks can personally require a re-examination of controversial patents. The U.S. Patent Office revoked Agracetus's cotton patent in 1994, but the issue is under appeal.

Revisions to U.S. Patent Law

As a result of World Trade Organization (WTO) negotiations, patent terms for applications filed on or after June 8, 1995, will extend 20 years from date of filing. Formerly, the term was 17 years from the date the patent was granted. Under the new provisions, companies have an incentive to accelerate the patent review process in order to get the most of the 20-year term. The former strategy was to delay the process to postpone the start of the 17-year period until the covered invention was closer to commercialization. This was of particular value to the pharmaceutical industry, which tended to divide the original application into separate applications, one for a product and another for that product's specified use. This practice enabled firms to first obtain a patent on a compound and then later a separate patent for use of that compound, thus effectively increasing the period of protection by several years. A delay in patent prosecution was particularly onerous for competitors, because in the U.S. patent applications are secret until the patent is granted, which could take up to four years. This procedure forces those firms that have developed the technology independently to obtain a licence from the patent holder. The U.S. Patent and Trade-mark Office has proposed limiting this advantage by publishing applications 18 months after filing. In response to the U.S. biotechnology industry, the House Subcommittee on Courts and Intellectual Property introduced a bill that would extend patent exclusivity past the legislated 20 years to compensate for delays in patent processing.

Higher Life Forms

Attempts to patent biotechnological inventions have challenged traditional patent law principles. The special nature of living matter and the ability to self-replicate distinguishes biotechnology from other fields. The U.S. Patent and Trade-mark Office granted a patent on a plant in 1985 and a transgenic animal (the Harvard onco-mouse) in 1988. To date, the U.S. has granted approximately 175 patents on plants, and there are more than 600 patents pending. Nine patents used in medical research have been granted but none yet on a farm animal. In Europe, plants may be patentable but plant varieties and traditional biological processes for the production of

plants and animals are excluded from protection. The EPO granted approximately 75 patents on plants and one patent on an animal, the Harvard onco-mouse, which patent is subject to opposition before the EPO. Japan has proceeded to grant patents on transgenic animals. The European situation is different because of the existence of Green or ecology parties in a number of countries and because of a specific provision in the EPC that can deny patents on public interest grounds. In addition, in Europe, notices of opposition may be filed for up to nine months after a patent is granted. No comparable statutory authority or procedure for objections exists in the U.S. or Canada.

In most EU countries, patenting decisions are broadly governed by the provisions of the EPC, to which some non-EU countries are signatories as well. Patent decisions under the EPC are made by the EPO. Since 1988, the EU has attempted to draw up a harmonized biotechnology patent system but in March 1995, the European Parliament rejected the proposed EU directive on "The Legal Protection of Biotechnological Inventions." The proposal codified principles for granting patents for genetically engineered plants and animals as well as the patentability of plant and animal varieties. Although many in the industry were in favour of a more clearly defined patent system, they also felt that the directive had become watered down because of numerous compromises. They preferred instead to work within the current system of EPO case law, filing through the EPO or with individual patent agencies. The EPO recently changed its interpretation of what constitutes a plant versus a plant variety (varieties are excluded from patentability under the terms of the European Patent Convention of 1973) by ruling that a patent granted to Plant Genetic Systems and Biogen for producing herbicide-resistant plants through genetic engineering cannot cover plants and seeds from the patented process. It is thought that the reason for the ruling might be a reinterpretation of the term "plant," which by definition could incorporate varieties and therefore be unpatentable.

Like Europe, the Canadian Intellectual Property Office has denied patents on higher life forms, cautiously interpreting patent law to provide protection only to new microbial life forms such as bacteria, yeast, moulds, fungi, algae, cell lines, viruses, protozoa, genes, plasmid, vectors and other nucleic acid fragments, but not to transgenic plants and animals. Processes for producing plants and animals that require significant technical intervention may be patentable, but traditional biological breeding techniques are not. There is no legislation specifically supporting this position, and court decisions are ambiguous.

While in the U.S. and Japan a plant variety may be patentable, this is not the case in Canada, which has limited the legal protection available to new varieties in certain plant categories via breeders' rights legislation. To stimulate plant breeding in Canada, to provide Canadian producers access to foreign varieties and to facilitate protection of Canadian varieties in other

countries, the *Plant Breeders' Rights Act* was proclaimed on August 1, 1990. The regulations initially provided protection for new varieties in the following categories of plants: canola, wheat, soybean, potato, chrysanthemum and rose. They have since been expanded to now include 39 crop categories (65 percent horticultural, for example, dianthus, poinsettia, and 35 percent agricultural, for example, strawberry, barley, flax). The Act provides a form of protection for new plant varieties that are distinct, uniform and stable. The rights holder can prevent others from selling or producing for sale in Canada, from propagating material of the new variety and from making repeated use of the protected variety to produce commercially another plant variety. Intellectual property protection in the form of plant breeders' rights is weaker than under patents because the rights extend only to the commercial trading of the reproductive material of the specific variety. Plant breeders' rights have important limits designed to facilitate continued improvement of protected varieties. Under a breeders' exemption in the Act, any protected plant variety can freely be used by others for the purpose of breeding other varieties; however, a U.S. patent provides an exclusive right to exclude all others from commercial exploitation of the invention. Another important feature is a provision that allows farmers to save or sell seed they have produced themselves for future planting, a possibility that U.S. patents would exclude. In Canada, plants *per se* are not patentable, but their genes and cell lines are.

Annex E
KEY FIRMS AND ASSOCIATIONS

Allelix Bio-pharmaceuticals is developing recombinant parathyroid hormone for treatment of osteoporosis, and is in phase I/II trials for treatment of cytomegalovirus (CMV) infection. It is also involved in research on various neurological diseases.

Alta Genetics is involved in the production and marketing of bull semen, cow embryos and research in embryo transfer and reproductive technologies.

Beak Consultants, **SENES Consultants** and **Biogénie** are leaders in the application of biotechnology for solving environmental problems.

Biochem Pharma has received FDA approval for 3TC for treating AIDS in combination with AZT and is pursuing work on the same product for treatment of hepatitis B. It also produces vaccines for the Canadian market and diagnostic kits for infectious diseases and associated laboratory instruments.

Biomira is developing colorectal and breast cancer vaccines and is marketing *in vitro* diagnostic tests for detection of breast cancer, sexually transmitted diseases and various hepatitis markers.

Cobequid markets aquaculture vaccines throughout the world.

Diagnostic Chemicals is a major supplier of diagnostic reagents and enzymes.

Hemosol is developing a line of cross-linked human haemoglobin products as red blood cell substitutes.

Microbix Biosystems manufactures infectious disease antigens for diagnostic kit manufacturers worldwide.

Pasteur Mérieux Connaught Canada, with research and manufacturing operations in Toronto and Pennsylvania, is Canada's largest producer of adult and pediatric vaccines and other biological products.

Phoenix International Life Sciences is one of the largest North American contract research organizations supplying clinical research and bio-analytical services to pharmaceutical and bio-pharmaceutical industries.

QLT Phototherapeutics has received approval for the use of photodynamic therapy in the treatment of bladder and esophageal cancer and is working on diseases of the skin and eyes.

SemBioSys Genetics is developing genetically engineered canola seeds carrying therapeutic proteins such as the anticoagulant hirudin.

Spectral Diagnostics has received FDA approval to market rapid format tests for the detection of heart attacks and other acute cardiac events.

The **Industrial Biotechnology Association of Canada** (IBAC) represents 61 organizations (26 bio-pharmaceutical firms, nine agriculture, 20 consultants, and six associations and government organizations) on national advocacy issues such as regulations and public awareness.

Regional associations include the **British Columbia Biotechnology Alliance** in Vancouver, **Ag-West Biotech** in Saskatoon, the **Toronto Biotechnology Initiative**, the **Quebec Association of Bio-Industries** in Montreal and the **Nova Scotia Biotech Working Group** in Centreville.

The **Canadian Institute of Biotechnology** in Ottawa, funded through Industry Canada's Technology Outreach Program, is involved in networking, biotechnology promotion and technology diffusion.