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Final Report

IMPROVING CANADIAN BIOTECHNOLOGY

REGULATION—

A STUDY OF THE U.S. EXPERIENCE

Prepared for

National Biotechnology Advisory Committee
Attn: Mr. G. Strachan, Chair

Chemicals and Bio-Industries Branch
Industry Canada
Attn: Dr. T. Walker

Submitted by

Garry Sears, Partner

Jac van Beek, Principal

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March, 1995
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This document represents the views of the members of the National Biotechnology Advisory Committee and KPMG Management Consultants, which views are based on extensive research in Canada and the U.S. by the Consultants. These do not necessarily represent those of the Federal Government.

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Acknowledgment

KPMG recognizes the contributions to this study of a network of Canadian and American associates providing scientific, legal and political experience and insight. The associates who worked with the KPMG team included, in Canada, Randall Goodfellow of Goodfellow Agricola Consultants, Linda Locke and Earle Nestmann of Cantox Inc., Joy Morrow of Smart and Biggar, and Barry Smith, an independent consultant. Our work in the US was assisted by Bruce Mackler of Fenwick and West, and Henry Miller of Stanford University.

We acknowledge the guidance and support of the National Biotechnology Advisory Committee and the Chemicals and Bio-Industries Branch of Industry Canada in the preparation of this report.

Highlights

In a comparison of US and Canadian biotechnology regulation frameworks, the basic building blocks were found to be remarkably similar. Regulations, for example, were not found to be significantly divergent—Canada was found to be more flexible and less complex, but requires more data. However, the American system was found to be more supportive of commercialization. Americans, it appears, have evolved a system of regulatory oversight that encourages business risk-taking and thus generates wealth. In seeking to uncover explanations, the study team was repeatedly drawn back to the dynamic forces that drive the American system and how agencies have come to apply the regulations.

Canada has a comparatively effective regulatory system for biotechnology-derived products. We now have an opportunity to emulate and improve upon American achievements and create advantage by providing a catalyst to stimulate the same forces in our society that have shaped the US system.

A. Key recommendations

The Minister of Industry is well placed to make a critical contribution to the biotechnology sector as the industry evolves towards commercialization—by encouraging efficient regulation. American experience indicates that scientific depth, public confidence, a strong industry voice and political leadership have all contributed to the efficient operation of a regulatory framework considered to be more complex than the Canadian regime. Specific recommended actions are focused upon fostering leadership, raising biological science literacy, accelerating equivalency and reciprocity and promoting regulatory 'best practices' designed to capitalize on the potential flexibility of the Canadian framework.

The Minister of Industry can make a major impact by:

- Stimulating industry coalescence and encouraging the emergence of industry leadership through discussions with industry associations and other industry representatives.
- Hosting a conference focused upon biotechnology and the public good.
- Increasing the general level of understanding of the issues of biotechnology by hosting a panel of both scientists and public policy experts to engage in a widely publicized discussion.
- Encouraging biological scientific education in our schools.

- Working with industry leaders to strengthen industry associations.

- Encourage establishment of test cases of agreements between Canada and the US (or other trading partners) on final product quality standards, preferably in an area of recognized Canadian competence.

- Encourage the identification and application of regulatory 'best practices' applying appropriate lessons from the US experience—especially the importance of science as a basis for regulatory policy—and the results of the test cases.

The National Biotechnology Advisory Committee is encouraged to endorse the recommendations and provide pilot test candidates for equivalency. Independent action, though well intentioned, is not expected to yield effective results.

B. Major Conclusions

1. American regulatory framework is more complex than Canada's

The United States has a complex set of laws and regulations at both the federal and state levels governing all aspects of the development and application of biotechnology-derived products. Canada's regime is similar but features fewer pieces of legislation, smaller and better linked regulatory agencies and a more collegial attitude.

2. Regulatory efficiency strategies based upon product-based risk

Efficiencies in regulating biotechnology respecting the need for safety, efficacy and environmental protection are being addressed in the US through applying well developed regulatory processes originally established for traditional products and boosting the ranks of reviewers. The costly and time-consuming process of creating new legislation and regulatory review and approval processes has been avoided through adoption of product-based risk assessment.

3. American regulatory advantage stems from several factors affecting the regulatory framework

Policies generally based on scientific principles, a sophisticated scientific infrastructure, public confidence, a strong industry voice and government support have all found an equilibrium that balances concerns for public safety, efficacy and environmental protection with the drive to recoup investment. In Canada, industry representation is small and fragmented and our scientific community has been less involved with critical issues relevant to biotechnology regulation—leaving our regulatory agencies with the balance of power and not as compelled to expedite review and approvals.

C. Major Findings

1. American biotechnology sector is maturing

The industry is moving rapidly towards widespread commercialization within the biopharmaceutical sector. Agricultural and food applications are expected to mature later because of the increased complexity of the intended results of research programs. Biotechnology has lost some attraction within the investment community as earlier claims of benefits either fail to materialize or fall short of forecasts. The continuing need for financing has led to widespread interest in building alliances, collaborations and partnerships with drug manufacturers who, in turn seek out new products.

2. Fast-paced technology is affecting the ability to regulate

As scientific discovery continues to outpace commercialization, responsibility for human and environmental safety must be shared between both industry and regulators. Excessive regulation can stifle commercialization and establishment of new regulations and review processes takes about a dozen years. The industry does not expect to work in an unregulated environment; conversely, regulators must recognize the limitations on their knowledge and the disincentive to wealth generation inherent in regulatory systems. A partnership between industry and regulators provides an opportunity for Canada to capitalize and accelerate the benefits of an emergent sector.

3. Regulatory frameworks are similar

Statutes, regulations and approval processes are not significantly different between Canada and the US. The two countries have a shared regulatory philosophy, operating principles and development of a co-ordinating framework. Both countries have also struggled with development of regulations in the environmental domain. Comparability extends to the regulatory agencies that have been established and their respective jurisdictions.

4. Key events showcase several differences

Several significant events have occurred in the evolution of the regulatory framework in the US that have not been emulated in Canada, including:

- Visible scientific debate.
- Public review of research.
- A court ruling supporting the patentability of life forms.
- A coalescence of industry associations resulting in a single voice for industry.

5. Product-based risk often undermined by belief in myths

The current wealth of scientific knowledge and experience provides sufficient evidence to support risk assessment policies based on products, rather than processes, whether they be conventional or involve recombinant DNA techniques. Recombinant-derived products can be accommodated within existing legislation. However, several myths undermine the principle and have contributed to an unnecessary tightening of application of regulations.

6. Case studies indicate greater flexibility in Canada

The experiences of firms that have had biotechnology products reviewed in both the US and Canada suggest that Canada's regulatory framework is potentially more flexible. This flexibility can be used to advantage, primarily to streamline requirements and focus resources on high risk products and the assessment of more complex data elements.

Flexibility, however, can be a double-edged sword, and requires supporting checks and balances to ensure the regulatory review process is predictable and consistent.

7. Canadian regulatory system has potential to be world leader

According to a limited sample of firms that have sought approvals in both countries, Canada:

- Has established a potentially more flexible regulatory framework that, for agri-food biotechnology products at least, could provide to be very effective. (Even the proposed CEPA regulations will allow companies to seek exemptions.)

- Has built the potential for flexibility into its regulatory system but has not demonstrated how this flexibility will be applied.

- Requires a higher level of detail (more extensive data) than the equivalent US regulatory agencies to support product submissions.

- Could be put at a competitive disadvantage because of the costs involved in obtaining product approvals in Canada, compared to the US.

Interviews with industry and government representatives suggests two other impediments to Canadian regulatory effectiveness:

- Canada has fewer resources and has less experience in regulating biotechnology products.

- A powerful industry voice or a supportive public constituency has yet to emerge that could influence regulatory policy and review positively towards biotechnology.

Comparatively higher approval costs in a country with a small domestic market could mean that companies choose not to invest in production in Canada, not to import otherwise beneficial biotechnology products, or seek product approvals outside of Canada and thus, focus their production and marketing efforts elsewhere. Without addressing the cost to industry of regulation, the country could potentially fall short on one of our guiding principles for regulating biotechnology; to: "Foster a favorable climate for development, accelerating innovation and adoption of sustainable Canadian biotechnology products and processes".

I

Introduction

A. Background to the study

The biotechnology sector is undergoing a transformation in this country, with the beginnings of a thrust into the global arena. Policy makers and advisors to government have undertaken a series of investigations and initiatives into ways of improving infrastructure and otherwise enhancing the ability of the Canadian biotechnology sector to compete the regulatory system is a major focus of attention.

The National Biotechnology Advisory Committee (NBAC), reporting to the Minister of Industry, provides an industry perspective on issues and believes current regulatory oversight in Canada to be a major challenge to the development of Canadian biotechnology. Through the Minister and by means of special initiatives such as the 1991 National Biotechnology Business Strategy, the Committee influences the development of the sector in Canada.

To encourage the growth and competitiveness of the emerging biotechnology industry, particularly the agri-food sector, a predictable, reasonable and responsive regulatory system is considered a prerequisite. These features are essential to assure investors that they should be doing research, development and commercialization in Canada. This is a particularly sensitive time, as Canadian subsidiaries of multinationals and smaller Canadian-owned companies are weighing the costs of regulatory clearance against the advantages of developing new products in Canada. These evaluations will determine whether conducting R&D and commercializing biotechnology in Canada are realistic activities.

Biotechnology R&D—both conventional and using the newer genetic manipulation techniques—is widespread, and has been generally well accepted by the public and the government, as have biotechnology products. However, as the industry continues to grow in importance worldwide and countries aggressively promote their own industry, Canada's biotechnology sector must capitalize on all its advantages in order to be a global player.

Canada has the potential to develop and implement the most efficient and effective regulatory system in the world, one which speeds products to market without compromising regulatory oversight. With this significant commercial advantage, the country could anticipate new investment, spawn new businesses, and growth and open up new and important trade opportunities.

B. Objectives and scope of the study

The objectives of the study were to:

- Describe the US regulatory framework and the actions over the past ten years that significantly contributed to the creation of that framework for biotechnology, with particular reference to agricultural, food and environmental applications.

- Define options for the Minister of Industry to consider in offering leadership for ensuring that effective biotechnology regulation in Canada is compatible with catalyzing and enhancing industry development.

- Define options for action for the Members of the NBAC that will lead to an improvement of the Canadian regulatory regime for the products of biotechnology.

The study limited investigations to specific application areas in biotechnology. Using the US experience as a baseline, we focused on an analysis of the processes in place, or that are imminent, and identified the process structures and guiding principles that could be readily applied in Canada. A number of factors and guidelines were also recognized in undertaking the required tasks and meeting study objectives:

- **Several types of biotechnology products were investigated**, each with a different set of regulatory guidelines and requirements:

  - **Veterinary biologics**—principally veterinary biologics containing genetically manipulated living organisms.

  - **Plant genetics**—genetically modified plants possessing genetic material that would not normally be present in the species, i.e., where a novel, specific genetic element has been consciously developed or introduced.

  - **Microbial pest control agents**—This is the active ingredient or the microbial entity to which the effects of the pest control can be attributed. The end-use product, which contains this agent, is a microbial pest control product.

  - **Microbial fertilizers**—Microbial supplements, which may be naturally occurring or genetically modified, to improve the productivity of plant growth and uptake of plant foods, e.g., the uptake of nitrogen or phosphate.

  - **Environmental applications**—There is growing use of biotechnology products for such applications as: bioremediation, microbial enhanced oil recovery, biomining, bioleaching, biofiltration, etc.

- **Biopharmaceuticals**—the application of biotechnology to human therapeutics represents the area of greatest experience.

- **Our investigation also compared products that have been through the regulatory process in Canada and/or the US.** The study focused on how proposed new structures and guiding principles will be implemented using case studies of products approved in both Canada and the US. Information relating to the time and cost factors associated with specific examples have been used to support or illustrate findings and conclusions, where applicable and where information can be publicly released.

- We also considered the political and social climate that gave rise to the respective regulatory frameworks—leadership and political strategies, key events and media coverage.

- We attempted to provide not only explication but also recommendations for ways that Canada can capitalize on its competitive advantages in the regulatory arena.

C. Methodology and approach

The study sought to isolate key features of the American regulatory framework, considered to be more supportive of innovation and commercialization, that could be applied to Canada. A literature review, supplemented by a series of interviews with leading American policy makers from past and present administrations, and leading Canadian policy makers and regulators yielded key findings. Case studies corroborated opinions and illustrated general findings. A detailed list of participants is provided in Exhibit I-1.

Exhibit I-1
Listing of interviewees and case studies

In America	In Canada	Case Studies
• Greg Simmons, V.P.Advisor on Domestic Policy • Raxhel Levinson, Office of S &T Policy • Terry Medley, USDA • Al Young, USDA • Arnold Foudin, USDA • Elizabeth Milewski, EPA • Mike Gough, Office of Technology Assessment • John Cohrssen • David Mckenzie, USDA • Jim Cook, USDA • David Giamporcaro, EPA • Bill Gartland, NIH • Nelson Wivel, NIH • Henry Miller, ex-FDA	• Keith Bailey, Health Canada • A Ridgway, Health Canada • P McKnight, Health Canada • Frank Welsh, Health Canada • Jean Hollebone, Ag/Food • Simon Barber, Ag/Food • Brian Morrissey, Ag/Food • S.W. Gunner, Health Canada • Bill Drennan, Health Canada • M.S. Yong, Health Canada • Kent Foster, Health Canada • Margaret Kenny, Ag/Food • B.S. Samagh, Ag/Food • John Smith, Health Canada • Susan Langlois, Hemosol • Des Mahon, EC • John Buccini, EC • Nigel Skipper, EC • Jim Martin, TBS • Don Stephenson, WED	• Zeneca (ecozyme) - David Gagnon • Calgene (FlavrSavr) - Don Emlay (US) - Keith Redenbaugh (US) • Monsanto - Jack Wearing - Ray Mowling - David Kowalczyk (US) - Bob Hamess (US) • Pioneer - Rod Townsend (US) - Larry Zeph (US) - Sarah Fielder (US) • Other Industry - Dan Polonenko, Philombios - Jim Beechey, Cyanamid

We conducted the following case studies of companies' experiences in obtaining, or seeking, product approvals in the US and Canada to add depth to our analysis and assist the formulation of our recommendations:

- Zeneca Bio Product's *ECOZYME*, an environmentally sound kraft pulp bleaching solution.
- Calgene's genetically-engineered *FlavrSavr*™ tomato.
- Monsanto's *Posilac/Nutrilac* recombinant bovine somatotropin (rbST).
- Pioneer Hi-Bred's herbicide-resistant Canola, which is resistant to imid-azolinone herbicides.

II

Profile Of The Biotechnology Industry

The biotechnology industry has built a strong scientific capability that is beginning to reap commercial benefits. As the promise of returns on more than a decade of research investment verges on realization, the industry is beginning to consolidate and to integrate particularly in the better funded pharmaceutical sector. However, with competition growing fiercer and funding shortages pushing integration and consolidation, regulatory efficiency matters more than ever.

A. State of the US industry

As the world leader in commercializing biotechnology, the US points the way to what will happen elsewhere, including Canada.

1. Scientific discovery outpacing commercialization

Biotechnology as an industry is less than twenty years old—the product of the synergy among several fields of biology. To date, the industry has made optimistic, often unfulfilled promises and has required large investments. While science has progressed to a better understanding of how the human body and disease work at the most basic level, scientific discovery represents just the very first step in a long and difficult process of launching a marketable product.

Science has made a series of important discoveries, including for example:

- The production of a number of therapeutic proteins for a number of prevalent diseases.
- Replacement of defective genes through insertion of healthy versions into human cells.
- Transplanting human genes into mice to mimic human disease in research animals.
- Insertion of human genes into cows to produce human proteins in their milk.
- Development of vaccines against important diseases (e.g., Hepatitis A and B).

- Development of diagnostic tests for major adventitious agents in blood products.

More dramatic discoveries will likely emanate from the mapping of the human genome, as well as the genomes of animals and major agricultural plants. In 1980, about 40 genes were known; the number now exceeds 6,000 and is rising at a rate of about one per day. Recent discoveries include new genes associated with cancer, osteoporosis, Alzheimer's disease and some forms of aggressive behaviour. The commercial possibilities are of course, endless—each new gene produces a protein and each new protein is a potential new drug.

2. An industry shakeout appears imminent

The fortunes of the industry are increasingly under scrutiny as market potential appears not to be keeping pace with either the rate or the significance of scientific discovery. The basis for the current financial crisis in biotechnology and the basis for alliance building is the disparity between the financial needs of product developers and the money available from financial backers. Biotechnology firms generally need 7 to 15 years and $50 million to $400 million to bring a new product to market. Even during the optimistic 1991 financial market surge, most publicly traded companies were only able to raise about three years worth of money—far short of requirements. Many companies are currently scaling back their number of employees and the number of products under development. At the present time, the following conditions appear to be converging:

a) A proliferation of companies

The number of US biotechnology companies has grown steadily. Two recent sources report an increase of almost two hundred companies between 1989 and 1993 (Ernst & Young, 1993) and the publication, Recombinant Capital reports the increase of publicly traded biotechnology companies has grown from approximately 100 in 1990 to almost 240 by 1994.

b) Several high profile failures

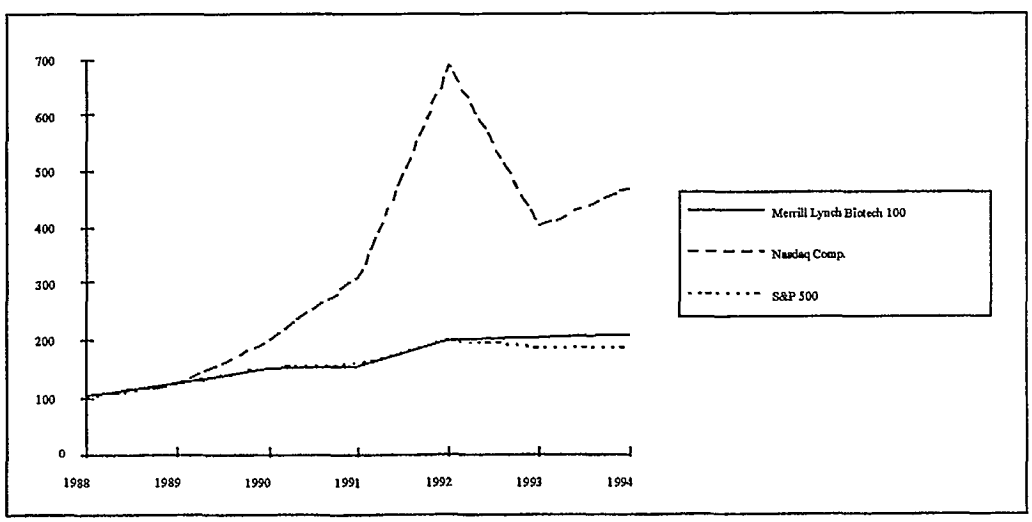
Several key high profile product development programs have failed. For example (see Exhibit II-1):

Exhibit II-1
Several examples of recent high profile failures in biotechnology

Company	Description of Failure and Date	Impact on Stock Prices
Centocor	Lethal side effects shelve drug in January, 1993Drop in stock prices of 76%	
Cortech	Sepsis drug failed to work, July 1994	Drop in stock prices of 86%
Glycomed	Shelves heart drug Astenose in May, 1994	Drop in stock prices of 91%
Magainin	Failure of skin infection drug in April, 1994	Drop in stock prices of 82%
Medimmune	Plans dropped to treat lung ailment in July, 1994	Drop in stock prices of 91%
Regeneron	CNTF, to fight ALS is disappointing in June, 1994	Drop in stock prices of 81%
Synergen	Hepatitis drug doesn't work	Drop in stock prices of 93%

The cumulative impact of the failures—coupled with the prospect of the Clinton health care program—has been a significant drop in the value of publicly traded stocks (see Exhibit II-2).

Exhibit II-2
Share prices for US Biotechnology Stocks



c) Funding support shifting to large firms

The allure of the industry to investors has fluctuated dramatically in recent years as Exhibit II-3 demonstrates. Private sources of capital have become more important to the biotechnology industry as public market contributions have flagged. One might infer that smaller companies' viability and strategic decisions about R&D made by all firms may be affected by the regulatory climate.

Exhibit II-3
US Biotechnology funding sources

Private sources of capital have become more important to the biotechnology industry as public markets' contributions have flagged. Amounts raised for biotech, in millions:

Source	1989	1990	1991	1992	1993
Initial public offerings	$300	$358	$1,188	$829	$527
Secondary public offerings	$400	$299	$2,515	$821	$931
Venture-capital firms	$102	$124	$200	$366	$411
Private debt	$82	$424	$445	$250	$455
Shares sold at a discount in private placements	0	0	0	$12	$413
Other*	$171	$39	$74	$374	$610
TOTAL	$1,055	$1,244	$4,422	$2,652	$3,347

** Includes licensing payments and other funding from partnerships with bigger companies.*

Source: Ernst & Young

d) Alliances are proliferating

The industry has witnessed a significant increase in strategic alliance and partnering activity driven by diminishing resources, complex technologies and soaring development cost requirements (consider that the cost of developing a new drug in the US is now approximately $359 million(US)). The predominant pattern at present is alliances between small, promising biotechnology firms which are capital-starved and large pharmaceutical firms which need new, innovative discoveries.

The extent to which large firms in the pharmaceutical sector have integrated alliances as a critical element of their strategies is illustrated by one corporate example in Exhibit II-4.

Exhibit II-4
Glaxo's strategic research alliances

Partner Company (Symbol)	Date Initiated (Extended)	Value of Deal ($M); Term (Years)	Equity (%)	Research Focus	Therapeutic Area
Allelix Biopharmaceuticals (TSE:AXE)	1988 (8/93)	N.D.	9.7%	Parathyroid hormone	Osteoporosis (Phase I/II trials)
Amylin Pharmaceuticals (AMLN)	10/91 (4/94)	N.D. (4 years)	None (joint venture)	Blockers of pancreatic hormone amylin	Type II diabetes (Phase I trials)
BioChem Pharma (BCHXF)	1990 (2/94)	N.D. (6 years)	17%	Nucleoside analogs	Anti-cancer and viral diseases, including 3TC for AIDS (in agreement with Wellcome) and 3TC (as lamivudine) for hepatitis B (in Phase III trials for both indications)
British Biotech pic (BBIOY)	7/92	N.D.	N.D.	Platelet-activating factor (PAF) antagonist (oral dose)	Asthma (anti-inflammatory) (Phase I/II trials)
Gilead Sciences (GILD)	8/90 (6/92)	$20M (5 years)	6%	Genetic code blockers	Cancer therapeutics, antivirals, other (undisclosed)
Icos (ICOS)	10/91	N.D.	N.D.	Phosphodiesterase (PDE) inhibitors	Inflammatory, respiratory, gastro-intestinal and cardiovascular diseases
Ligand Pharmaceuticals (LGNDA)	9/92	$10M (5 years)	6%	Hormone-activated intracellular receptors	Atherosclerosis

Exhibit II-4
Glaxo's strategic research alliances (cont'd)

Partner Company (Symbol)	Date Initiated (Extended)	Value of Deal ($M); Term (Years)	Equity (%)	Research Focus	Therapeutic Area
MegaBios (private)	4/94	N.D. (5 years)	N.D.	Gene therapy	Cystic fibrosis
Neuro-Search A/S	1/93	N.D. (5 years)	N.D.	High-conductance calcium-activated potassium channel blockers	Central nervous system disorders
Regeneron Pharmaceuticals (REGN)	7/93	$10M	3%	Neurotrophins (brain-derived neurotrophic factor and neurotrophin-3)	Neurological and psychiatric disorders
Sequana Therapeutics (private)	7/94	N.D. (5 years)	N.D.	Genetics/genomics	Type II diabetes
Spectra Bio-medical (private)	6/94	N.D. (3 years)	N.D.	Genetics/genomics	Migraine

3. Still waiting for big returns in agriculture

Despite a decade of intense research, genetic engineering is just beginning to score significant commercial triumphs in agriculture. Mapping and moving plant genes is taking longer than expected, and in some respects, is proving more complicated than in humans. In some respects, plant breeders face greater challenges than those creating drugs in microorganisms and cultured mammalian cells. Single-gene transfers in plants do not produce as scientifically or commercially important results, and the molecular biology of plants lags far behind that of microorganisms and mammalian cells.

Moreover, the complexity of the challenge is hampered further by the relatively modest research funding being allocated to agriculture (about 5% of US federal research funding vs 42% to human health) and market resistance towards the initial technology 'push' products—the current driver in agricultural biotechnology. Consumer benefits are not driving development and commercialization programs in the sector at present. Several areas of aggressive development include:

- rbST (recombinant bovine somatotropin), a genetically engineered version of a hormone that a cow's pituitary gland makes to regulate milk production is now available to increase milk production.
- FlavrSavr™ tomatoes genetically altered to improve taste by inserting a copy of the gene that inhibits rotting.
- The quest for plants that can tolerate environmentally-friendly herbicides.
- Molecular probes, or flags, are making it possible to mark the location of genes and thus allowing conventional breeders to determine if they have passed on traits in both plants and animals.

Based upon applications for field trials in the US, most plant research has been directed primarily towards herbicide resistance with significant interest in insect resistance, altered product quality and virus resistance, and some interest in fungal and/or bacterial pathogen resistance.

4. Promise of a bright future in biotechnology

Scientists are still seeking to achieve breakthroughs that would ensure a robust future for biotechnology. Some notable examples include:

- Self-fertilizing plants based on enabling crops to fix their own nitrogen from the atmosphere.
- Protein pills capable of withstanding the body's digestive system.

- Nerve regeneration.
- High speed chemistry using catalysts that work at the speed of enzymes and under the same mild conditions.
- Slow aging through discovery of the gene which prevents cell death.
- Gene therapy for AIDS, hyperchloresterolemia, or other prevalent diseases.
- Production of vaccines in plants, so that immunization could be conferred by consuming fruits or vegetables.

The biopharmaceutical sector is maturing with some winners and some firms are considered to be on the brink of commercial success (see Exhibit II-5):

Exhibit II-5
Biopharmaceutical winners and potential winners

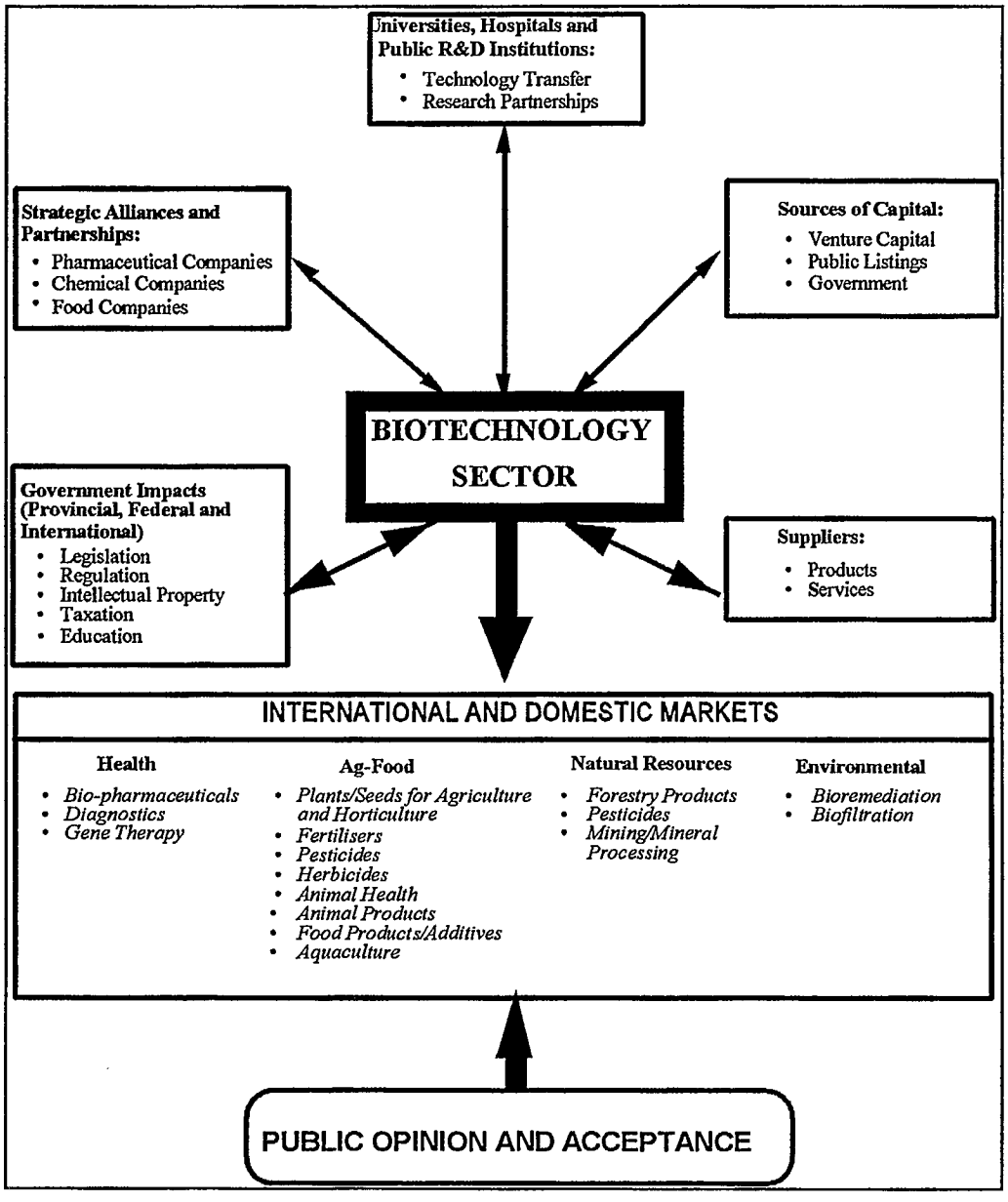
Winners	Potential Winners
Amgen—*EPO* to fight anemia and *Neupogen*, an immune stimulator *1993 Revenues of $1,500 million/earnings of $383.3 million*	**Cor Therapeutics**—Conducting pivotal trials on *Intergrelin*, to treat disorders that follow heart attacks
Biogen—*Alpha interferon* for hepatitis and cancer; Hepatitis B vaccine; diagnostic technology *1993 Revenues of $149.3 million/earnings of $32.4 million*	**Biogen**—Testing *Beta interferon* to slow progress of multiple sclerosis
Chiron—Hepatitis tests (licensed to Ortho); *Interluken-2*, an anticancer agent; *Betaseron*, a multiple sclerosis drug *1993 Revenues of $317 million/earnings of $32.4 million*	**Centocor**—Awaiting approval of *ReoPro* to prevent blood clots **Celtrix**—Completing key tests on *Betakine* to treat macular holes, a condition of the eye that leads to blindness
Genentech—Human growth hormone; *TPA* for heart attacks; *Gamma interferon* for a childhood immune disorder; *DNAase* for cystic fibrosis *1993 Revenues of $649.7 million/earnings of $58.9 million*	**Genzyme**—Testing *Thyrogen* as a treatment for thyroid cancer and hyaluronic acid as a product for surgical adhesions **North American Vaccine**—Awaiting key data on a new vaccine for childhood diseases such as pertussis
Genzyme—*Ceredase* and *Cerezyme* for Gaucher's disease *1993 Revenues of $274 million/earnings of -$6 million*	**Telios**—Awaiting approval for a wound-healing product **Cellpro**—Awaiting approval on a cell-separation system to aid in bone marrow transplants **Univax**—Awaiting approval on *WinRho*, a potential blood-disorder treatment

B. Issues of the Canadian biotechnology industry

As products of the new biotechnology near commercialization in Canada, the impression exists that the number and complexity of issues facing the biotechnology sector may be increasing. But this is not necessarily the case. The absolute number of products in the pipeline is small and, if new biotechnology is regarded as simply a subset of various classes of products—vaccines, new plant varieties, drugs and so forth—with no unique regulatory requirements (vide infra), the incremental burden need not be great.

Being an enabling technology, biotechnology can be applied in a wide range of industries to develop new products and improve existing ones. Issues facing the sector are driven by decisions and actions in other areas of the economy that may appear, on the surface, to be quite distant from the commercial application of biotechnology, as shown in Exhibit II-6.

Exhibit II-6
Driving forces in the biotechnology sector



III

Evolution Of The American Regulatory System in Comparison with Canadian Experience

The American biotechnology regulatory regime has evolved in parallel with the maturation of the technology. The Canadian experience has been to follow the same general path without progressing through the catalytic events of scientific community introspection, public debate or political leadership.

Rather than re-construct the events that culminated in the respective regimes of the two countries, a selection of events were highlighted to ascertain whether progress has been roughly parallel or whether there has occurred a 'parting of ways'. While there have been lags in development, the two countries have been surprisingly similar in the evolution of their respective regulatory frameworks.

A. 1970's—Start-up of the industry

1. American experience—Regulation as a form of "self-induced disease"

Safety concerns about recombinant DNA technology were raised shortly after the first successful genetic transfer experiment. The pioneering scientists declared a moratorium on recombinant research until the issue of oversight could be reviewed. They organized the Asilomar Conference to reach a general agreement within the biotechnology research community about what should be done. The National Institutes of Health (NIH) was the first federal agency to claim regulatory jurisdiction over genetic engineering processes in NIH-funded research, specifically. In 1976, National Institutes of Health (NIH) issued guidelines designed to ensure safety in biotechnology research. The first guidelines, adopted in a burst of enthusiasm and self-congratulation, were strict; but as scientists re-examined the paradigm and learned more about the safety of genetically modified organisms, the guidelines were repeatedly revised and the controls on recombinant DNA research in the laboratory were modified.

Towards the close of the 1970's, the tremendous economic growth in the US made available a significant pool of venture capital seeking investment opportunities. A convergence of technology, researchers and capital fueled a twenty-year growth of small technology-driven companies utilizing biotechnology to develop high value added products with the promise to investors of sizable financial returns.

An early pivotal event in the evolution of US biotechnology policy was the NIH funded Asilomar Conference that explored the risks and benefits of recombinant DNA. The Conference, involving leading researchers of the day, offered a series of recommended guidelines for the conduct of research. In the absence of definable risks, the guidelines were stringent. In retrospect, it is evident that the expertise of those who recommended and crafted the Guidelines was lamentably narrow. Had there been representation of fields such as medical bacteriology, evolutionary biology, and allergy -- who could have shed light on questions outside the realm of molecular biology -- overly burdensome guidelines might have been avoided entirely. In any case, they would unquestionably have been much less stringent.

NIH adopted the Guidelines and, in 1974, organized the Recombinant DNA Advisory Committee (RAC) to review and oversee recombinant DNA research proposals. In 1976, NIH (through the RAC) produced the NIH Guidelines for Research Involving Recombinant DNA Molecules. Thus the first policy initiative in the US was driven by the (unrealistically narrow) scientific debate, followed by rapid adoption by a government agency. Government used the lever of research funding and public review to ensure adherence to prescribed procedures, and thus established an initial approach that addressed public and Congressional concerns about the need for oversight to prevent disasters. The lifting of the moratorium on research, which followed the promulgation of the Guidelines, facilitated the flourishing of research groups.

As research activity migrated to industry from government and academic sectors, there was a voluntary adoption of the NIH guidelines by firms and their researchers.

2. Self-imposed guidelines vs expansion of funding for research

The cumulative impact of the Berg Letter (the initial challenge issued to the research community to oversee research), Asilomar Conference, establishment of the research guidelines and the RAC was to catalyze scientific debate. RAC in particular provided a platform with credibility and integrity. The existence of RAC had two positive impacts:

- A platform for diverse opinions delayed the need for and the consensus necessary for enacting federal legislation.

- A public forum was provided to assess and assimilate new advances in the science.

Throughout this same period, the focus of the Canadian research community was to mobilize resources and secure government support. The Strategic Technologies program of National Sciences and Engineering Research Council (NSERC) and establishment of the National Research Council (NRC) biotechnology research program occurred in the early 1980's.

The Canadian Medical Research Council (MRC) adopted the American NIH model in the late 1980's. Canada, thus effectively avoided the open debate, public controversy and self-examination which helped to shape the American regulatory framework.

Exhibit III-1 provides a brief selective summary of events that transpired in the two countries.

Exhibit III-1
Key events in early development of biotechnology

Key events suggest a different early world view of technology

US	Canada
• Berg Letter issued a challenge to the science community to self-police biotechnology	• Government increased R&D effort in biotechnology -Strategic Technologies
• Asilomar conference (1975) reponded by proposing research guidelines	
• Recombinant DNA Advisory Committee(RAC) (1976) and system of local safety boards estblished	
• NIH funding for research tied to guideline adherence (1976)	• Government investment in biotecnology research programmes - NRC, Ag and Agri-Food Canada
	• MRC adopted guidelines during late 1980's with the concurrence of the reaearch community (modelled on US)

3. Regulatory structures and framework followed similar evolutionary paths

It is difficult to focus on any single event in the evolution of the regulatory framework. In the American experience, a series of events contributed to policy development. The FDA Points to Consider (technical guidance documents), focused on biologics, yet provided a format that has been adopted by other agencies. Points-to-Consider documents provided flexibility and allowed agencies to promulgate quasi-guidelines without engaging the lengthy rule-making process.

The Co-ordinated Framework provided a central coordination framework for the review of all government biotechnology regulations to determine appropriateness. When published in the Federal Register in December, 1984, it provided an index of US laws related to biotechnology, and:

- Clarified the policies of the major regulatory agencies involved in the review of research and the products of biotechnology.

- Described a scientific advisory mechanism for the assessment of biotechnology issues.

- Explained how the activities of the federal agencies in biotechnologies are to be co-ordinated.

The ABC Report on cell line and biologic product importation resulted in a significant reduction in administrative delays and costs to the entire industry. Subsequently, biopharmaceutical products, reagent monoclonals and field testing of genetically engineered organisms were included. Each signaled a new agency consensus which led to additional agency movement on other products as they assuaged inherent safety concerns.

One event provides the most significant difference between the two countries. The *Chakrabarty* decision upholding the patentability of new life forms created the security in intellectual property protection which assured investors of product exclusivity in the marketplace. Investors were more receptive to financing ventures. The lack of protection for higher life forms discouraged investment in Canadian enterprises. The industry, in Canada, has grown relatively more slowly and has, to date, failed to coalesce into a powerful voice able to lobby effectively for regulatory improvement.

Canadian events lagged to some extent but mirror the establishment of the US regulatory framework. Two notable differences include the principle of 'single window' product access and the proposed framework for novel foods and processes (already included in existing US legislation).

A summary of key events are listed in Exhibit III-2.

Exhibit III-2
Key events in evolution of regulations

A sample of regulatory and commercialization events suggest that Canada is "catching up"

Key Events in US	Parallel Events in Canada
A. Evolution of Regulatory Framework and Structure	A. Evolution of Regulatory Framework and Structure
1983	1986
- Points to Consider Document	- Coordinated Study on Government Processes in Safety/ Regulation of Biotechnology
1984-86	1988
- Coordinated Framework for Regulation of Biotechnology	- Cabinet Directed Agencies to Develop Coordinated System
- Ice-Minus Field Testing Permit	1992
1986	- Basic Principles of Federal Framework Using Existing Legislation/Providing "Single Windows" for Product Access
- USDA Revision of DNA/Hybridoma Cell Line Importation Restrictions	1988
1988	- Ice Nucleating Protein for Snowmaking Approved Under Environmental Contaminants Act
- USDA Policy for Field Trials of Biotechnology-Based Products	1994
1992	- Timeframe for finalizing regulatory Guidelines for Ag/Food Biotechnology
- FDA Statement of Policy on Foods Derived from new Plant Varieties	- "Building a More Innovative Economy"—Accelerate Regulation/Guideline Development
B. Protection of Intellectual Property	1995
1980	- Additional Regulations in Seeds, Feeds, Fertilizers, Pest Control Products, Health of Animals and CEPA Recognizing Biotech Products with Traditional Counterparts
- Diamond vs. Chakrabarty	1992
	- HC Information Letter 806: Proposed framework for novel foods/processes
	B. Protection of Intellectual Property

B. Early 1980's—Positioning for commercialization

A series of events converged to shift the focus of biotechnology from research to commercial development during the 1970's and 1980's. American researchers, to secure NIH grants, had to demonstrate applied utility. Thus scientists were becoming increasingly aware of the potential commercial value of their research. The salaries of scientists stagnated and universities sought supplemental research funds from licensing of research results. Once venture capitalists were assured of patentability, investment funds lured academic researchers into technology-driven biotechnology firms.

In Canada, research was conducted primarily in government laboratories funded by grants. The impetus to create strong relationships with industry and the venture capital community did not emerge until the late 1980's as deficit reduction became a key driver of strategy in government.

1. Rapid company formation and growth of industry associations

In the early 1980's, the number of "biotechnology" companies that used recombinant DNA to develop products increased exponentially in the US. The investment in such

companies was fueled by favourable tax regulations, limited partnerships, patentability of new life forms, and the perception of riding a new technological wave within a generally expanding economy.

Between 1978 and 1988, hundreds of companies were established. Initially, these companies supported two trade associations: the Association of Biotechnology Companies (ABC) and the Industrial Biotechnology Association (IBA), which eventually merged in 1993 to create the Biotechnology Industry Organization (BIO). Larger companies participated in IBA, while smaller companies gravitated to ABC along with service providers, government agencies and international firms. Both associations grew, to 120 members for IBA and 460 for ABC before the merger. The association now represents a formidable voice for the industry. Some 2,700 delegates attended the May 1995 BIO conference in San Francisco.

In Canada, the Industrial Biotechnology Association of Canada (IBAC) plays a similar role to BIO, though many other organizations in specific application areas provide a fragmented series of voices. A variety of regional biotechnology interest groups exist across Canada, each concerned with various aspects of promoting and facilitating the commercialization of biotechnology in their jurisdictions. IBAC has yet to define working relationships with these groups.

A similar situation exists in relation to other industry interest groups, such as the research networks like BIONET and industry promotion organizations like the Canadian Institute of Biotechnology (CIB). These organizations' programs complement the work of IBAC but this mutually beneficial role has yet to be translated into effective networking.

2. Establishment of a regulatory framework

As the focus of activity migrated out of laboratories towards commercial development, the US government sought to prescribe a regulatory framework for biotechnology-derived product development. The practical choice facing framework designers was whether to promulgate new laws and regulations or use the existing legal matrix. Canada lagged in development of the framework primarily because industry has not grown to the same extent and because commercialization potential did not become apparent until later.

The US legislative system normally requires several years to formulate, achieve political consensus through debate and enact laws. Once enacted, regulatory agencies require two to four years under the Administrative Procedures Act (APA) to publish proposed interpretative regulations, receive public comment and publish the final regulations in the Code of Federal Regulations (CFR). Even after the final issuance, there is characteristically a lapse of two to three years to understand how regulations would be applied, triggering publication of guidance documents. In the absence of legal challenges by public activists or industry groups, the entire process requires approximately five to ten years.

The rapid advances of biotechnology could not be accommodated within this

timeframe. Thus legislators faced the conundrum of following process at the expense of retarding commercial development. Concurrently, rapid technological advances on many fronts placed into doubt the wisdom of new law creation paralleling new scientific advances—commercial development could literally grind to a halt.

A small group of middle level officials—Dr. Henry Miller, John Cohrrsen and Dr. David Kingsbury—mounted a conscious initiative to utilize the existing matrix of laws and statutes to provide sufficient oversight. The underlying rationale was acceptance of biotechnology-derived products as equivalent to existing products developed by traditional technologies, for purposes of oversight. Canada adopted the same approach several years later within the regulating agencies and largely without the leadership of strong advocates.

Thus, by focusing on end-products, existing legislation in key areas of application have provided the cornerstone of American policy towards oversight of biotechnology. Environmental Protection Agency (EPA) has asserted legalistically that its existing statutes were too vague and legally inappropriate to address the risks of biotechnology. Consequently, the Agency has been seeking to create new legislation aimed specifically at biotechnology.

Key existing legislation addressing issues of commercialization—patents, tax credits, export and import—have also accommodated the products of biotechnology. Canada has yet to parallel these US initiatives.

3. Scientific advance and regulatory framework development

Until the mid-1980's, all experiments with genetic manipulation were conducted in controlled laboratory or greenhouse environments. However, in the fall of 1983, biotechnology arrived at a critical and potentially volatile turning point as scientists at University of California at Berkeley prepared an experiment that would deliberately release a newly created organism into the environment. It was not until 1987 before researchers at Advanced Genetic Sciences Ltd. applied an altered bacterium to strawberry plants in the first government-sanctioned environmental release of a bioengineered microorganism.

Much of the controversy and legal maneuvering over biotechnology in the 1980's centred on whether scientists could prove that the release of a biologically-altered organism would not harm the environment or people. It was not until 1987 that a resolution became possible—the National Academy of Sciences (NAS) issued a report saying that there was no scientific evidence that organisms containing recombinant DNA pose unique hazards. The report said that while a panel of scientists concluded that strict controls on bioengineered materials were not justified, regulation of large-scale releases of such organisms was needed. The NAS panel said that to realize the potential benefits of genetic engineering, a balance must be struck between the thrust of innovation and the restraint of regulation and oversight.

4. Public interest and regulatory framework development

With the exponential growth of the industry, there was a rise in sensitivity amongst public advocate groups to the risks of recombinant DNA technology. As the public debate intensified, Congress and relevant federal agencies debated their roles and how best to ensure appropriate oversight.

Public debate has been vigorous in the US for the past twenty years. Public activists have been part of on-going debate through the evolution of RAC. Public debate has continued throughout the period of intransigence of EPA to adopt a consensus government policy. Alarmists provided sufficient fuel to prompt establishment of the President's Cabinet Council on Natural Resources and the Environment which sought to promulgate a Co-ordinated Framework for Regulation of Biotechnology, providing an index of US laws related to biotechnology and how such products should be regulated.

Canada has to this point avoided wide public debate. Recent events centred around opposition to rbST and questions over genetic screening would suggest that public concerns are on the rise.

A summary of some significant events in the two countries are provided in Exhibit III-3.

Exhibit III-3
Key events in development of the industry

A sample of regulatory and commercialization events suggest that Canada is "catching up"

Key Events in US	Parallel Events in Canada
C. Market Introduction 1982 - Approval of DNA-Based Products: Insulin, Growth Hormone, Monoclonal Antibodies 1993-94 - FDA Licenses Use of BST (With No Required Labelling) - FDA Licenses Flavr Savr	C. Market Introduction 1985-1990 - Approvals of Initial "Home Grown" Products, e.g., Philom Bios Biomal and PB50 1994 - Approval of rBST in Canada (Standing Committee on Ag and Ag Food) on hold with one year moratorium 1995 - Flavr Savr Import Approved
D. Public Acceptance 1983-1990 - Mild "Technophobia" and anti-biotechnology advocacy/ lawsuits	D. Public Acceptance Mid-1990s - Escalation of Public Debate
E. Industry Growth 1980-1990 - Rapid Company Formation and Establishment of Trade Associations - Increasing Access to Capital 1990s - Consolidation—Mergers/Acquisitions/Alliances - Investor Confidence Diminishing (health reform) - Continued Low Investor Confidence—Ag./Env.	E. Industry Growth 1980-1990 - Establishment of small firms, associations and committees NBAC, IBAC, CIB

5. US Regulatory Agency co-ordination

In 1984, the President's Council on Natural Resources and the Environment established an interagency working group to study and coordinate the government's regulatory policy for recombinant DNA-derived products. The results of interagency collaboration were published in the US Federal Registry as a Proposal for a Co-ordinated Framework for Regulation of Biotechnology (Fed Reg., 49(25):50856, December 31, 1984). A revised document was published in 1986, which described the "comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products" (Fed Reg., 51(123):23302, June 26, 1986). To facilitate implementation and application of this policy, the White House established the Biotechnology Science Co-ordinating Committee (BSCC).

C. Late 1980's—Positioning for regulation

While the umbrella of BSCC appeared to provide a sufficient basis for co-ordination, each federal agency with regulatory responsibilities pursued separate agendas:

1. Food and Drug Administration (FDA)

FDA experienced the first commercial applications for the marketing of products utilizing recombinant DNA technology. During the early 1980's, FDA had accumulated more experience with products of the new biotechnology than the world's other regulatory agencies, combined. In addition to a steady stream of applications to begin testing therapeutic drugs and vaccines, the agency was deluged with applications for the marketing approval of diagnostic kits (based either on rDNA techniques or on monoclonal antibodies derived from hybridomas). The FDA policy was, from the outset, that new biotechnology techniques were extensions, or refinements, of older genetic techniques -- and therefore, new biotechnology products would be subject to no new requirements, regulations, or procedures. FDA did produce various technical guidance documents called Points to Consider. These provided information to regulators about such issues as the use of continuous cell lines for drug production, acceptable levels of impurities of products obtained by fermentation, and so forth.

2. US Department of Agriculture (USDA)

USDA, which regulates plants, animals, animal therapeutic vaccines and diagnostics, meat and products and seeds, is structured as a set of subagencies all pursuing somewhat autonomous goals and priorities. The Department also had a strong tradition of separating agricultural research and regulation; and USDA regulators were not known for a strong scientific orientation. Not surprisingly, USDA's formulation of policy was often unscientific and marked by scientific principles caught between empire-building and turf battles. Attempts to centralize decision-making have foundered on bureaucratic ineptness and the absence of policymakers at the highest levels who understood or cared about biotechnology.

USDA's Animal and Plant Health Inspection Service (APHIS) has developed technique-based regulations under the Plant Pest Act that have had several adverse effects on R&D. They have vastly increased the expense of performing field trials (10-100 fold, compared to plants with identical characteristics but engineered with conventional, less precise techniques) and have captured for regulation field trials that most experts agree should be exempt. (All 1800 of the permits issued by APHIS for field trials of recombinant plants have been for experiments of negligible risk.) While the number of field trials performed by industry has risen continuously under this regime, the number of experiments performed by public-sector organizations (which traditionally perform the most innovative research) has been stagnant.

The Science and Education part of USDA -- distinctly separate from the regulatory part where APHIS is located -- has tried for years to establish an unnecessary new regulatory agency within the Office of Agricultural Biotechnology (OAB). Its purview would be field research with transgenic animals created with rDNA techniques. OAB's efforts have been clumsy, unscientific -- and unsuccessful.

3. Environmental Protection Agency (EPA)

EPA is widely recognized as the bete noire of US regulatory agencies. Over more than a decade, EPA attempted to articulate a biotechnology regulatory policy. Continually bucking the scientific consensus and official federal policy, EPA returned again and again to proposals that would specifically regulate only rDNA manipulated organisms, both microorganisms and plants with pesticidal properties. EPA has been widely criticized for unscientific policies generally and lacking or misusing scientific advisors. The sectors that EPA regulates -- microbial pesticides, plants with disease- or pest-resistance, bioremediation -- are widely felt to have been damaged (decreased R&D, diminished investor interest, few commercialized products) by uncertain, unscientific, non-risk-based regulation.

D. Present state of development

The present American biotechnology framework is heterogenous in both its approaches and its results. FDA has had a largely transparent and equitable regulatory approach, many products have moved into and through the system, and investor interest has been substantial. FDA has prepared but not yet released a proposal that would require registration of biotechnology-derived foods. It now appears unlikely that the FDA will be permitted to release this policy.

The NIH RAC shares with FDA responsibility for regulating human gene therapy proposals. The reviews are largely duplicative and while there appears little advantage to the NIH's involvement, old regulations -- and regulatory agencies -- die hard.

USDA operates with new (1987) technique-based regulations under the Plant Pest Act (and more restrictive procedures for biotechnology-derived biologics under the Virus-Serum-Toxin Act). USDA has been gradually removing various plants from the

requirement for a permit for field trials, substituting a notification. While this represents progress of a sort, the basis of USDA's entire approach remains unscientific and the basis for eligibility for the notification, illogical.

Consistent with the Clinton administration's inclinations to regulate biotechnology heavily, the EPA continues to churn out proposed and final regulations under both the pesticide statute (FIFRA) and the toxic substances statute (TSCA). The Congress will examine these new regulations in hearings during this session and may well overturn or revise them legislatively.

While in theory the regulatory system operates within a co-ordinating framework, application of regulations is the responsibility of three generally autonomous government agencies. While products spanning more than one jurisdiction may require co-ordinated review, typically companies must work within the approaches adopted by the agency with prime responsibility.

US governmental policy towards biotechnology has never reached a uniform consensus but rather has evolved into several fairly independent entities with shifting alliances and scientific considerations and public pressures variously shaping the approaches of the agencies responsible for oversight. The US biotechnology policy exhibits a zig-zag evolutionary path, buffeted by Congressional oversight, public advocacy groups and bureaucratic disputes. The dynamic of these forces has in the past shaped policy and its application. As each new administration assumes power, policies are re-cast based on political pre-delictions and prior prejudices.

IV

Comparing Regulatory Frameworks

The regulatory frameworks covering biotechnology applications in both Canada and the US are somewhat parallel—both provide a rational process that assures safety, efficacy and weighs the costs to the environment against the benefits to society. The Canadian system, however, offers less complexity and, potentially, more flexibility—better suited to an industry reliant on fast evolving science and technology, and better designed to speed products to market.

A. Key concepts and definitions

1. Product vs process-based risk

Regulatory frameworks and application of specific policies are, in theory, related primarily to factors such as the potential risk of various products to the public health and environmental safety, and the quality and sometimes efficacy of those products. (The European Union has also considered including a "fourth criterion," socio-economic considerations.) But some policies, such as those of USDA and EPA (as contrasted to FDA) have implemented regulations that have a technique-specific trigger.

Putting this another way, biotechnology policies may be divided according to whether they are either:

- *Product-driven,* with the application of regulations and effort triggered by expectation of risk inherent in the product (for example, according to lists of organisms that require permits) or for certain uses (human vaccines);

or

- *Process-driven,* with the application of regulations and effort triggered by the expectation that the use of the new biotechnology is inherently unpredictable and that products made thereby must be stringently regulated "case by case every case" (perhaps with limited exemptions) until risks are better known.

Process- or technique-driven regulatory regimes have often been liberalized on the basis of "experience" with field trials or "risk assessment" experiments. However, the reasoning for these regulatory modifications has often been specious (Miller reprints: Trends in Biotechnology., 1994; The American Enterprise), the regulatory agencies

seeking a pseudo-scientific "fig-leaf" for regulatory evolution.

Application of a product-based regulatory policy focuses oversight where risk is considered "unreasonable" while application of a process-based regulatory policy results in virtually automatic, risk-independent (and often burdensome) oversight of any product developed using the new biotechnology.

2. Potential addition of socio-economic considerations

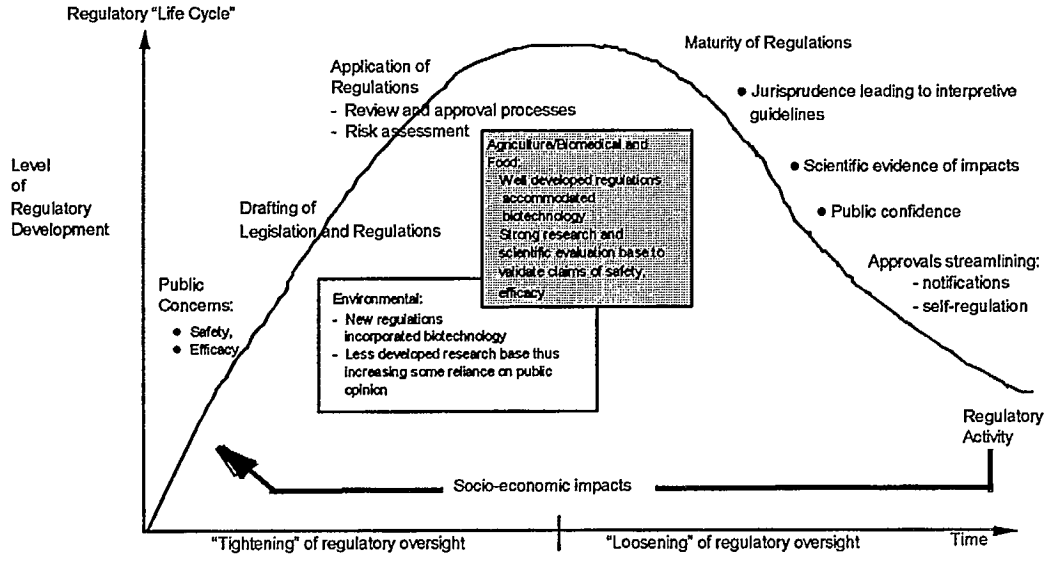
More recently, the regulatory debate has been broadened, to consider the inclusion of a "fourth hurdle"—socio-economic impacts and benefits. This issue is a variation of the argument that *"if it's biotechnology, it must be inherently harmful (to the social and economic structure of society)"* as no other products have to demonstrate socio-economic efficacy. (Although, new drug products are being subject to a similar type of evaluation in an increasing number of jurisdictions—pharmacoeconomic evaluations—before they can be added to formularies and added to drug benefit lists.)

Regulatory agencies, accustomed to the technical and statistical focus of current product evaluations, are uncomfortable with the notion of socio-economic evaluations. They have (rightly) sought to have these issues addressed as matters of government policy.

3. Stages of regulatory development

Development and application of regulations appears to follow a somewhat predictable pattern, driven to a large extent by the *desire* of regulatory agencies to arrogate new responsibilities and by governmental perceptions (often misperceptions) of public perceptions. We have summarized the pattern in Exhibit IV-1.

Exhibit IV-1
Stages of regulatory development



Applying the model provides two insights:

- The environmental sector is not in the same position as the other sectors we have considered in the study.

- Positioning on the 'curve' can change as new information surfaces (systematic adverse effects or the results of bona fide risk assessment experiments) or products undergo fundamental change (development of biotechnology-derived pharmaceuticals) or experience a crisis event (death through use of a regulated product) and risk rises.

B. American regulatory framework

The first wave of biotechnology-derived products emerged in the biomedical sector primarily because of their high return potential. Thus FDA became the pioneering agency in applying regulations to the new technology.

FDA used existing regulations, imposed no new requirements, focused on product characteristics and expedited review and approvals at the earliest time that safety and efficacy were demonstrated. An underlying understanding of biotechnology based on a strong scientific capability integrated with regulators made such an approach possible. The Agency also assessed new risks introduced by biotechnology products within well understood categories, amassing information on a case-by-case basis, and summarizing

experience in 'Points to Consider' documents. Since these documents were not regulations, they could be changed as quickly as the technology changed—circumventing the normal 5 to 10 year legislative and rulemaking process.

USDA adopted a similar scheme accepting that agricultural and forestry products derived from biotechnologies will not differ fundamentally from traditional products.

EPA felt that legislative jurisdiction was weak, and did not cover new biotechnology-derived microorganisms that were: used in the environment; pathogenic or contained genetic material from other pathogens; or contained new combinations of traits. EPA's desire to develop explicit legislative authority transcended the regulatory flexibility exhibited by other agencies. Underlying the legalistic formality is the EPA's desire to have a 'process-based' regulatory policy which inherently presumed a greater risk because of the use of biotechnology even in the absence of any definable risk. EPA has adopted a 'case-by-case every case' approach to assess safety and utility of products.

1. Regulatory focus is on control of demonstrated risk

The US is the world leader in scientific and technical development of the new biotechnologies, witnessed, for example by the number of new biotechnology companies and level of inward investment. The American government has strongly advocated that regulation should be based on demonstrated risks, and not turn on the fact that an organism has been modified by the use of particular processes.

2. General philosophy is regulation of product

The US approach is based (in theory, as noted above) on the principle that neither genetic modification generally nor the use of a specific technique(s) need trigger regulation. Simply stated, the philosophy is that many of the agricultural and agri-food products of genetic engineering do not pose an incremental risk to human health or the environment than similar products that have not been genetically engineered. The President's Council on Competitiveness report on national biotechnology (1991) stated that "regulatory oversight should focus on the characteristics and risks of the biotechnology product, not the process by which it was created."

3. Regulatory authority—contained use

The purpose of "contained use" regulations assure laboratory or workplace safety for "contained uses" of organisms. Containment is achieved by physical means (e.g., fermentor vessels or cabinets) and biological means (e.g., reduced viability) supplemented by chemical means (e.g., disinfectant). Levels of containment are generally specified for systems falling into various different categories.

A voluntary registration and notification system is operated by the NIH non-federally-funded rDNA research. For federally funded research, the procedure is obligatory, and guidelines issued by the NIH are used. NIH has an expert recombinant DNA Advisory Committee to review higher risk federally funded research (which is virtually non-existent) as well as human gene therapy protocols. Assessment of lower

risk experiments is conducted by Institutional Biosafety Committees (IBC's), which are a long standing and important part of the regulatory system.

In practice, despite the NIH's technique-based mandate, more than 99.9% of laboratory experiments are exempt from the NIH Guidelines, and therefore there is virtually no additional burden in practice for rDNA research.

The Centers for Disease Control and the NIH have issued a handbook the provides voluntary guidelines for the laboratory use of microorganisms. It is significant that this handbook does not discriminate in any way between "genetically engineered" and "natural" organisms; that it includes the most pathogenic organisms known; and that these guidelines are voluntary.

Industrial applications are the responsibility of several bodies including Department of Health, the Food and Drug Administration and the Occupational Safety and Health Administration (OSHA, located within the Department of Labor), and sometimes the EPA.

States may enact additional regulation, although this has been rare (moreover, several states that have experimented with their own regulations, have repealed them or permitted them to "sunset").

4. Regulatory authority—deliberate release

The purpose of regulation of planned introductions is to protect both human health and safety and the environment from the risks associated with the deliberate release of genetically modified organisms into the environment or their marketing. A variety of organizations regulate genetically modified plants and animals under the authority of pre-existing legislation—some new regulations have been necessary. A sample includes:

a) United States Department of Agriculture

USDA regulation of plants is administered by the Animal and Plant Health Inspection Service which regulates through a issuance of permits, primarily under the Federal Plant Pest Act (for rDNA-modified organisms that contain DNA from plant pests) or the Virus, Serums, and Toxin Act. Plants constructed using biologic methods are unregulated unless federally funded (NIH and USDA guidelines apply). The Inspection Service also operates a 30 day notification system for the inter-state transport of other genetically modified plants. Prior to marketing, a genetically modified plant must be granted a non-regulated status under the above laws through a petition procedure.

Animals considered to be plant pests could, in theory, be controlled under the Federal Plant Pest Act. Genetically modified animals derived from infectious, contagious, pathogenic or oncogenic organisms could be subject to regulation under the Animal Quarantine Statute and the Virus-Serums-Toxin Act. Federally funded releases would be regulated by NIH guidelines.

There is currently no control over fish, though the USDA operates a voluntary system of review, advised by its Agricultural Biotechnology Recombinant DNA Advisory Committee.

USDA regulates animal vaccines under the Virus-Serums-Toxin Act.

b) US Environmental Protection Agency

EPA is consulted for its view under the Federal Insecticide, Fungicide and Rodenticide Act regarding any plant with pesticidal activity. EPA also regulates genetically modified microorganisms under the same act and Toxic Substances Control Act.

c) National Institutes of Health

Under NIH guidelines, all deliberate releases of rDNA-manipulated organisms for research and development purposes, except for certain plants, require review and approval (but they are exempt if reviewed by another federal agency). Furthermore, any experiment which might involve the transfer of a drug resistant trait to microorganisms which are not known to acquire it naturally and which could compromise the use of the drug in human or veterinary medicine, has to be approved. While NIH guidelines apply to federally funded research, compliance with them is voluntary in the private sector.

5. Key acts and regulations

Several critical statutes have had a major impact on the ability of US biotechnology firms to develop and market products derived from biotechnology.

a) Federal Public Health Service Act

Biological products are regulated under section 262(a) of the Act, which has not been altered since 1906. The statute is the most flexible in handling biotechnology-based products. The wording of the statute and the interpretative guidelines provide a flexible basis capable of accommodating issues. Scientific issues are dealt with by the Centre for Biologics Evaluation and Research and the Points to Consider documents based on experience, provide guidance. Extensive pre-submission consultation and accessibility to FDA staff have allowed for expedition of reviews and paperwork.

b) Federal Food, Drug and Cosmetic Act

The Act regulates products, not technology, per se (although it considers various aspects of techniques, such as the source of a drug, the purification process, and so forth). During the FDA approval process, the Agency focuses on the overall safety and effectiveness of the product. Through flexibility and foresight in regulating biotechnology products, it has not been necessary to develop new regulations or rules. New Drug applications usually take two to four years for approval. FDA has changed its regulations recently to allow for 'fast track'

approvals for those drugs which have shown high therapeutic benefit for life-threatening and serious diseases. Additionally, treatment IND's have been developed to provide open-label studies of promising drugs, and to allow manufacturers to recover cost for providing the drug.

c) Medical Device Amendments to the Federal Food, Drug and Cosmetic Act

The first FDA approvals of new biotechnology-derived medical devices were for in vitro diagnostic devices incorporating monoclonal antibodies. In the early 1980's several manufacturers sought to substitute monoclonal antibodies for polyclonal rabbit antibodies. The Division of Clinical Laboratory Devices was the early focal point for biotechnology-based products. The policy adopted was to emphasize the analyte as the determining regulatory issue rather than the process used to develop the product. The use of the 510(k) approval process enabled companies to demonstrate 'substantial equivalence' of their products with those incorporating traditional technologies, and thus allowing a 90 day review. The same policy has been applied to the approval of gene probe technology for the first Legionella diagnostic. Novel technologies have been subjected to more rigorous review.

d) Orphan Drug Act

The Act was originally enacted to stimulate the development of drugs and biologics to treat patients with rare diseases (a disease that affects less than 200,000 people in the US or a disease for which there is no reasonable expectation of developing a drug and/or recouping development costs). The Act provides a tax credit for development and clinical trial costs as well as seven years of market exclusivity in the marketplace.

e) Drug Export Act

The Act provides that finished drugs awaiting US marketing approval can be exported to 21 countries listed in the statute. The Act provides biotechnology companies with international commercial opportunities during their development stage—alternative funding sources.

f) Patent Act

The Act has been extended to include microorganisms as a manufacture or as a composition of matter (established in *Chakrabarty vs. Diamond* ruling in 1980). The scope of patentable subject matter now also includes non-naturally occurring, non-human, multi-cellular living organisms, including animals.

g) Agricultural Statutes (plants)

Agricultural applications of biotechnology to plants are governed by several laws: Plant Quarantine Act, 7 USC 151-167; Federal Plant Pest Act 7 USC 150; and the Federal Noxious Weed Act 7 USC 2801-2813. Under these acts USDA

regulatory scheme consists of general and specific permits, quarantines and other methods of preventing or limiting the movement of plants.

h) Agricultural Statutes (animals)

Development and marketing of certain animals—beef and poultry—(including transgenics) is regulated under the USDA statutes pertaining to the slaughter and consumption of meat for food use as regulated by the Federal Register Meat Inspection Act and the Poultry Products Inspection Act. Within the framework, the Food and Safety Inspection Service has been developing guidelines and criteria for reviewing such products. USDA has also been assessing whether transgenic animals represent new breeds or merely animal husbandry efforts to change an existing breed.

i) FIFRA and TSCA

The Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act have been under the jurisdiction of the Environmental Protection Agency since the early 1970's. FIFRA is a licensing statute that confers jurisdiction upon EPA to regulate the distribution, sale and use of pesticides in the US. The Act requires that all new pesticides be registered (approved) by EPA before commercialization. To be considered safe, use of a pesticide may not result in unreasonable adverse effects on the environment. The ultimate decision on safety rests on a balancing of risks and benefits.

The EPA has proposed an anomalous approach for various non-pesticidal uses of microbes. For example, products which are formed by deliberately combining genetic materials from organisms of different genera of nonindigenous bacteria are subject to more stringent controls than intrageneric (somehow supposedly more "natural") combinations.

TSCA, which took effect in 1977, was intended to fill gaps left by other statutes. It gives jurisdiction to EPA over the manufacturing, processing, distribution, use and disposal of all 'chemical substances' or mixtures thereof in commerce or intended for commerce that are not covered in other statutes. That definition has been interpreted to include microorganisms. Except for rDNA-manipulated microorganisms, regulated products are subject to a small-scale exemption defined as "small quantities solely for R&D."

Companies do not need approval to manufacture but must notify EPA of their intent to manufacture, import or process a new chemical substance at least 90 days before processing begins. Because TSCA is a notification statute, EPA must affirmatively act to prohibit a substance being manufactured.

C. Canadian regulatory framework

1. Establishment of the regulatory framework has lagged behind commercial development of agricultural and environmental biotechnology products

Regulatory assessments of anticipated commercial biotechnology products have been undertaken on a case-by-case basis, to date. As in the US, two of the three key regulatory agencies—Agriculture and Agri-Food Canada (AAFC) and Health Canada—have sought to review biotechnology products using existing legislative and regulatory structures, which were designed for products produced using fine chemical processes or traditional plant breeding technologies.

2. General principles for regulation were established in January 1993

In Canada, the basic principles of the regulatory framework for the biotechnology products were defined in the Regulatory Framework for Biotechnology approved by Cabinet and announced in January 1993. Six principles were formulated to ensure that "... biotechnology products undergo thorough environmental and human health and safety assessments before release to the environment and/or commercialization":

"1. Maintain Canada's high standards for the protection of human health and the environment.

2. Build on existing legislation and institutions, clarifying jurisdictional responsibilities and avoiding duplication.

3. Develop guidelines, standards, codes of practice and monitoring capabilities for pre-release assessment of the risks associated with release to the environment.

4. Develop a sound scientific database, upon which risk assessments and evaluations of products can be made.

5. Promote development and enforcement of Canadian regulations in an open and consultative manner, in harmony with national priorities and international approaches.

6. Foster a favorable climate for development, accelerating innovation and adoption of sustainable Canadian biotechnology products and processes."[1]

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[1] *Government of Canada, **Backgrounder—A Federal Regulatory Framework for Biotechnology**, January 11, 1993.*

3. Deadline for formalization of the regulatory framework was established in May 1994

Regulations and guidelines for the evaluation of agri-food and environmental biotechnology products have been undergoing development for some years, e.g., work on the regulations for microorganisms, under the requirements of the Canadian Environmental Protection Act (CEPA) started in 1987. The three federal departments with primary responsibilities for regulating biotechnology—Agriculture and Agri-Food Canada, Health Canada and Environment Canada—have conducted extensive stakeholder consultation programs to obtain feedback on proposed regulations.

However, much of this work was being undertaken without any specific end-date in sight, which gave rise to concerns (especially as the pace of commercialization was accelerating) within the biotechnology industry and at the political level. In response to these concerns, a deadline was set for finalizing the proposed regulatory requirements in Spring, 1995, to permit *Canada Gazette* publication process (Parts I and II) to be finalized in the summer of 1995. The Deputy Minister at Western Economic Diversification, Janet Smith, is widely recognized as providing the impetus to resolve this issue, as well as setting actions in train to resolve questions of jurisdiction between departments, e.g., for undertaking reviews of environmental safety.

4. Key departments and legislation

Regulations and guidelines for the evaluation and approval of agri-food and environmental biotechnology products nearing finalization, having been recently published in the *Canada Gazette, Part I*, or with publication pending. The key regulatory departments are:

a) Agriculture and Agri-Food Canada (AAFC)

AAFC is responsible for: plants with novel traits; veterinary vaccines and biologics; fertilizer supplements, including microbial supplements with novel traits; novel feeds; and microbial pest control agents.

b) Health Canada

Health Canada is responsible for evaluating the safety of novel food products and human and animal drugs. It is also intended that the department will undertake the human health aspects of biotechnology products being reviewed under the Canadian Environmental Protection Action (CEPA) New Substances Notification Requirements.

c) Environment Canada

Environment Canada, in conjunction with Health Canada, will be responsible for assessing the health and safety of biotechnology products coming under the "catch all" provisions of CEPA (i.e., CEPA applies to those products not expressly regulated under other Acts). The main products that will be regulated under CEPA are environmental management and resource recovery applications of naturally occurring and genetically modified microorganisms, and biopolymers and biochemicals.

d) Industry Canada

Industry Canada, in addition to having a mandate to foster the industrial development of the biotechnology sector, is responsible for the administering of labelling and advertising claims under the Food and Drugs Act, and the assessment of patent applications.

Exhibit IV-2 lists the principal federal Acts applicable to biotechnology products.

Exhibit IV-2
Major components of the Canadian biotechnology regulatory framework

Lead Department	Application
Health Canada	
Food and Drug Act	Applies to all human and veterinary drugs (includes pharmaceuticals produced by recombinant DNA technology), food, food additives and contaminants, medical devices and cosmetics.
Hazardous Products Act	Covers hazardous consumer goods. The Act is administered by Industry Canada (formerly Consumer and Corporate Affairs) on the advice of Health Canada.
Agriculture and Agri-Food Canada	
Animal Disease and Protection Act	Regulates veterinary biologics (e.g., vaccines), animal products and by-products.
Feeds Act	Regulates livestock feeds and ingredients.
Fertilizer Act	Regulates fertilizers and supplements.
Pest Control Products Act	Regulates pest control agents (including genetically engineered products).
Plant Quarantine Act	Deals with all varieties of plant pests.
Seeds Act	Regulates new varieties and forms of seeds (including genetically engineered products).
Environment Canada	
Canadian Environmental Protection Act (CEPA)	Proposed New Substances Notification Requirements will be administered jointly by Environment Canada and Health Canada. The Act will regulate the manufacture or importation of all "new" toxic substances (as defined in the Act) not controlled under other statutes. Information must be provided before manufacture or importation takes place.
Industry Canada	
Canadian Patent Act	Administered by the former Department of Corporate and Consumer Affairs, now located within Industry Canada. The ability to patent higher life forms is being pursued with the Patent Commissioner's office, to enable Canadian and Canadian-based firms to operate in a competitive global environment.

The federal components of the regulatory framework are augmented by provincial regulations. We have included the Ontario regulations as an example of the provincial regime in Canada (see Exhibit IV-3).

Exhibit IV-3

Major components of the Canadian biotechnology regulatory framework—Ontario as an example of provincial coverage

Regulating Body	Application
Ontario Ministry of the Environment	
Environmental Protection Act	Regulates the addition, deposit, emission or discharge of any contaminant into the environment.
Ontario Water Resources Act	Requires prior approval for proposed facilities with emissions to air or water, or which are intended for waste disposal.
Pesticides Act	Complements the federal statute, and regulates the sale, use, transport and disposal of all pesticide products in Ontario.
Ontario Ministry of Labour	
Occupational Health and Safety Act	Delineates the duties of employers to inform, instruct and supervise workers for the protection of health and safety, and applies to biotechnology hazards in addition to other manufacturing activities.
Ontario Ministry of Agriculture and Food	
Animals for Research Act Artificial Insemination Act Plant Disease Act Milk Act	These acts contain policies on issues such as microbial pesticides (target is to reduce the use of chemical pesticides by 50%), as well as a number of statutes.
Ontario Ministry of Health	
Health Protection and Promotion Act	Directed to the prevention, elimination or decrease of health hazards.
Ontario Drug Benefit Program	Indirectly affects the commercialization of pharmaceutical products by controlling which products will or will not be covered by the government drug plan.
Ontario Ministry of Natural Resources	No statutory control over biotechnology products but is very interested in biological pest control.

The main concern arising from a brief assessment of this framework is the number of players, the apparent overlap in jurisdiction and the potential for conflict amongst regulating bodies seeking appropriate positioning. Within such an environment, a lack of consistency in approach or philosophy will have a detrimental effect on our ability to be competitive.

The importance of actually following through on applying scientifically defensible, risk-based regulation cannot be over-emphasized: the creation of regulations or discrete regulatory approaches specific to genetically modified organisms is both contrary to scientific consensus and certain to damage Canadian R&D and the Nation's competitiveness.

D. Points of comparison

While the developmental paths in the two countries have differed in timeframe or in the process that was followed, there are many comparative features.

1. Similar agencies and their respective jurisdictions

The two countries have developed roughly parallel regulating agencies with similar jurisdictions as illustrated in Exhibit IV-4.

Exhibit IV-4
Agencies with jurisdiction over biotechnology

Both countries have established parallel regulating agencies with similar jurisdictions

US Agencies	Jurisdiction	Lead Canadian Agencies
Food and Drug Administration	Food and Food Additives including Food Colours** Food Safety Human and Animal Drugs* Medical and In Vitro Diagnostic Services Human Biologics: vaccines, serum, toxoids, viruses	Health Canada
US Department of Agriculture	Plants, Seeds, Feeds, Fertilizers Animals and Animal Products* Agricultural Commodities (Fruits, Vegetables, Dairy Products Animal Biologics Animal In Vitro Diagnostic Biologicals	Agriculture and Agri-Food Canada
Environmental Protection Agency	Microbial Pesticides*** Non-Agricultural Microbial Agents* Chemical Water, Air and Wastes Contained Microorganisms*	Environment Canada

* *Shared responsibilities amongst agencies in Canada. Drugs, vaccines and food uses are regulated by FDA*
** *Including foods produced by rDNA technology.*
*** *In Canada, primary responsibility for registration rests with AAFC.*

2. Comparative legislation

While specific acts do not completely overlap, there is a high degree of comparability between the legislation in place for the key application domains of biotechnology (see Exhibit IV-5).

Exhibit IV-5
Comparative legislation

Key legislation is similar-accomodating (not targeting) biotechnologie

US Acts	Domain	Canadian Acts
Federal Noxious Weed Federal Meat Inspection Federal Poultry Inspection Virus, Serum and Toxic Plant Quarantine Plant Variety Protection Federal seed Federal plant Pest	Agriculture	Seeds Feeds Fertilizer Pest Control Products Plant Protection Health of Animals Canada Agricultural Products Plant Breeders' Rights Act
Toxic Substance Control Federal Insecticide, Funcidide &Rodenticide Resource, Condervation & Recovery Marine Protection Research and Sanctuaries Clean Air Super fund	Environment	Canadian Environmental Protection
Federal Food, Dug and Comestic Public Health Service	Foods, Drugs, Cometics and Medical Devices	Food and Drugs
National envirnmental Policy Executive Order 11987-"Exotic Species"	Other	

3. Shared philosophy and principles

The respective roles of regulations and the marketplace in Canada are well articulated in a recent response to the Standing Committee on Agriculture and Food report on rbST:

> *" The standard procedure in Canada and other industrialized countries is to regulate products based on scientific principles. Products are assessed for safety, and effectiveness. Once safety and effectiveness have been reviewed, it is the marketplace in Canada which then decides on the market acceptance of the product, based on benefits such as price and individual values and preferences."*

Government response to the Standing Committee on Agriculture and Food's report on rbST

American philosophy and principles are similar (the stated philosophy and supporting principles are summarized in Exhibit IV-6).

Exhibit IV-6
Stated philosophy and supporting principles for the regulation of biotechnology

Canada and the US

Philosophy	Principles*
• Biotechnology will contribute substantially to improved health care, agricultural efficiency and the amelioration of many pressing environmental problems • Regulatory oversight can assure that applications of biotechnology do not adversely affect the environment and public health and welfare	• Use existing legislation and eliminate duplication • Eliminate unneeded regulatory burdens for all phases of developing new biotechnology products • Government oversight should be only that which is necessary and sufficient • Federal government oversight should focus on the characteristics and risks of the product—not the process by which it is created • Risk assessments and evaluations should be based on sound scientific data • For products requiring review, review should be designed to minimize regulatory burden • Regulatory programs should be designed to accommodate rapid advances

* US—President's Council on Competitiveness (1991)
Canada—Federal Regulatory Framework (January 1993)

4. Parallel lag in regulatory development of environmental sector

Both countries are struggling to establish scientific principles as the basis for regulating biotechnology-derived products introduced into the environment. Both EPA and Environment Canada appear to be out of step with the general philosophies and practices of biomedical, agriculture and food regulators— and the countries' scientific communities as well. In both Canada and the US, a process-based philosophy appears to guide actions. Several underlying factors have been offered by officials we interviewed in both countries:

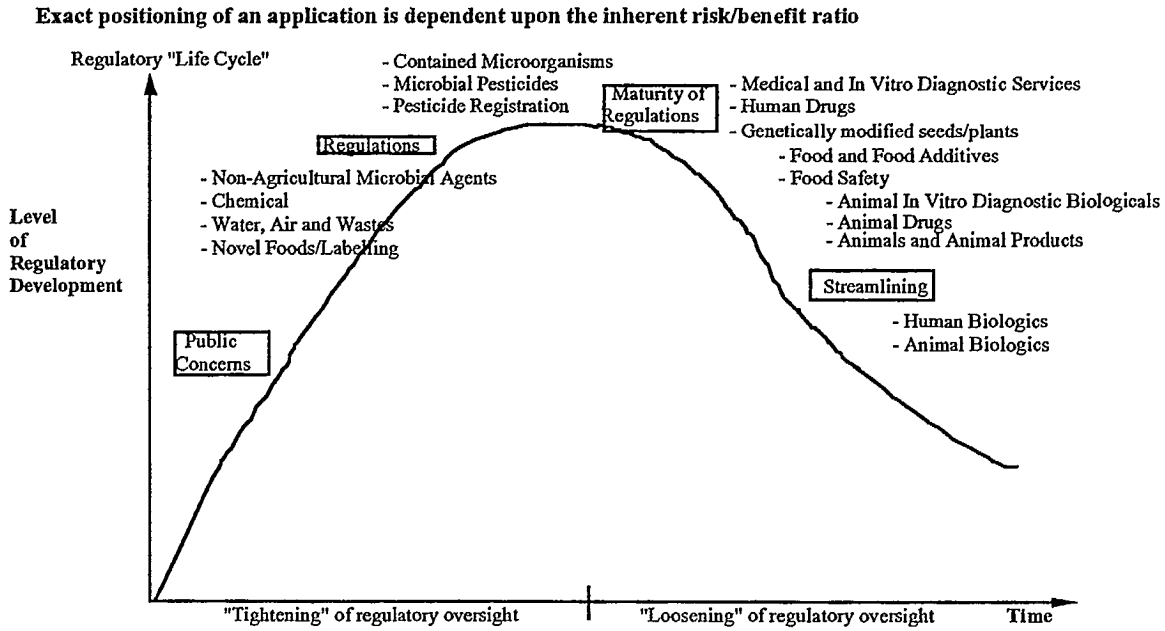
- **Impacts of biotechnology-derived products on the environment are not understood.** While the impacts of biotechnology-derived products used in field trials are not as highly predictable as those of laboratory research, risk analysis is certainly highly developed. The vast experience with organisms of many kinds, both tested and used outside containment, and the enviable safety record of agriculture, bioremediation, live vaccines, etc. argue that risk analysis for these applications is adequate.

- **Environmental assessment processes are well developed—but don't satisfy some environmentalists.** As noted above, risk analysis procedures exist and are generally adequate for environmental testing and use of a multiplicity of organisms and applications. However, radical environmentalists who are suspicious of or hostile to new technology often do not like the result.

- **Science has not yet been linked with regulation in the environmental area** —partly because of the underdeveloped state of ecological sciences and partly because of the origins of environmentalism as a populist cause, rather than as a science-based discipline. There is no satisfactory rationale for disparate regulatory requirements for products with similar or identical products, depending only on the techniques used for their production -- particularly when the more precise and predictable techniques are subject to a greater degree of scrutiny.

To verify our observations, several of those interviewed placed specific product categories on the model of regulatory development introduced in Exhibit IV-1. Exhibit IV-7 confirms that assessed risk appears to be higher when regulatory oversight is considered to be relatively immature.

Exhibit IV-7
Relationship between risk and 'tightness' of regulatory oversight



E. Points of divergence—application of policy

In a review of application of stated policies in the two countries there is an apparent difference in approach.

1. Application of policy in the US

Closer examination of some examples puts into question whether the US actually adheres to the stated principles (see Exhibit IV-8).

Exhibit IV-8
Examples of applied policy in the US

Application of policy appears to be inconsistent with intentions

Policy	Some Examples of Actual Policy
Risk-based, scientifically-defensible, product-oriented oversight	Plant Pest Act Regulations • Federal permit system for field trials and transport generated 1800 permits including risk assessments for organisms of negligible risk • Reform— USDA: substitute notification for permits in limited circumstances (too narrow and based on specious reasoning) White House: considered removing rDNA focus, then backed off EPA • Actual review: burdensome, unscientific, politicized • Ice-minus subjected to onerous review because of classification as a pesticide despite low risks • Proposals where scope of regulation has turned on use of techniques • Preference is for a centralized approach—all rDNA manipulated bio control agents would be subjected to review after which there would be a decision whether the experimental use permit regulations are applicable USDA • Did not pursue guidelines—now a "vertical" mechanism for oversight of field trails subject to jurisdictions of various agencies FDA • No new procedures/requirements • New proposal requiring notification for biotechnology (foods) in preparation

2. Application of policy in Canada

In Canada, application of regulations appears to be more consistent with stated principles except in the case of environmental regulations (see Exhibit IV-9).

Exhibit IV-9
Examples of applied policy in Canada

Policy	Some Examples of Actual Policy
Risk-based, scientifically-defensible, product-oriented oversight	AAFC—Seeds, Plant Protection, Pest Control Products, Feeds Acts • Approach based on evaluating intended end-use(s) (not process based), and application of risk assessment principles to screen products (e.g., herbicide-resistent seeds are "high risk") • Single window service; AgCan manages inputs from other departments (other AAFC groups, Health, Environment) • Has potential for flexibility, as regulatory experience develops • Resource levels and "client orientation" critical to effectiveness of implementation Environment Canada—CEPA • Risk assessment equated with geographic scope of use and whether organism involved is indigenous to the ecozone of use • Minor differences in data requirements between notification groups (i.e., from use in a confined facility through to use anywhere in Canada) • Canadian requirements characterized as "zero risk" orientation vs. US "risk-benefit" orientation • But, CEPA has provisions for data exemptions. Health Canada—Veterinary Drugs • Flexibility/discretion in review process can reduce predictability and objectivity in review process, and no "referee/arbitrator" to resolve process issues (e.g., data issues) • rBST experience suggests non-regulatory political issues (socio-economic impacts) can delay approvals • Potential scope for recognition/acceptability of data from US field trials.

F. Case study insights

Four case studies were conducted to supplement our interviews with representatives of key US and Canadian regulatory agencies and industry stakeholders. These case studies examined the experiences of four companies in taking biotechnology products (a bioenzyme, animal drug, herbicide-resistant seed, and genetically engineered food product) through the applicable regulatory processes in the US and Canada. Collectively, all of main federal regulatory agencies in both countries—USDA, EPA, FDA, AAFC, Health Canada and Environment Canada—were involved in these product assessments.

Taken together, these case studies provided a number of valuable insights and comparisons into the way regulatory processes actually operate in practice. These insights added depth to our analysis of guiding principles and regulatory policies drawn from the Canadian and US interviewing programs.

1. Canadian approaches could represent better applications of risk assessment and product-focused approaches

As we have noted elsewhere in this report, the principles and philosophies underlying the regulatory frameworks for biotechnology in the US and Canada share many similarities, not least being the intended focus on product characteristics in the review process. A number of participants in the case studies suggested that the approaches

underlying Canadian regulations are more consistent with the principles of product-focused risk-based assessment, e.g., Canada's approach on seeds versus the US Plant Pest Act.

2. Canada offers greater potential for flexibility, but often has more demanding data requirements to start with

Canada's regulations offer the potential for greater flexibility on the part of reviewers to vary data requirements to reflect the particular characteristics and risks associated with different types of biotechnology products. This approach recognizes that risk assessments, and hence data requirements in submissions, reflect insights gained from increasing familiarity (among regulators and researchers) with a new product's performance, traits, uses and environmental effects, assessments of substantial equivalence.

However, it is too early too tell if Canada's flexibility will be exercised (and there are currently no mechanisms in place to determine if, and when, data requirements can be reduced). This potential flexibility contrasts with the more prescriptive approaches of the US regulatory agencies, which require every step and data requirement to be "checked off".

On the downside, the initial "risk levels" set in Canadian regulations require more extensive data (in the form of additional testing or more extensive field trials) to be compiled to support product submissions, compared to the US agencies. The proposed CEPA New Substances Regulations (versus TSCA requirements) are one case in point but similar comments were also made regarding products falling under other Acts and regulations.

3. Regulatory flexibility is a double edged sword

The prescriptive approach that is more common in the US has the advantage of ensuring that data requirements are known and common for all companies developing similar products. In contrast, Canada's more flexible approach could be less transparent and less predictable, leading to inconsistencies in the treatment of different companies seeking approvals of similar products. Flexibility will only be effective if there are suitable checks and balances to ensure sound guidelines are established and consistently applied.

4. Accessibility and a strong client orientation plays an important role in moving submissions through the regulatory agencies

The quality of interactions between regulatory agencies and companies with products in the review process plays an important role in ensuring submissions are prepared correctly and reviewed expeditiously. The participants in the case studies expressed satisfaction with the overall handling of their submissions in both systems, recognizing that, in several cases, their products were "guinea pigs" for testing and fine tuning the applicable review processes. Two points in particular were emphasized as being important to the establishment and maintenance of a professional and responsive

working relationship during the review process:

- An ability to initially meet with the regulatory agencies and determine the precise nature of the data required to support product submissions and understand the scientific rationale for requesting such data. Thereafter, maintaining a professional working relationship throughout the review process became paramount, not to seek "favourable treatment" but to review and resolve any scientific issues that arise.

- A commitment on the part of the regulatory agencies to be responsive to their clients and to process submissions expeditiously without resorting to artificial means of extending review periods. The USDA and FDA were rated particularly highly on their client orientations.

5. Canadian regulatory agencies will have insufficient resources to handle the anticipated volume of, and detail in, product submissions in coming years

One of the advantages Canadian regulatory agencies offer to biotechnology companies is that the agencies are relatively small, it is easy to understand how they are structured, and determine who to deal with. Unfortunately, the resources will be insufficient to process the volume of product submissions anticipated in coming years, and the amount of detail that may be required in each submission. In contrast, many of the US agencies have been able to increase the resources available to handle biotechnology submissions and are able to provide high quality, responsive client service.

6. A higher level of scientific interchange could facilitate the evolution of Canada's regulatory framework

A number of the participants in our case studies, and interviews with industry representatives, noted that scientific interchanges (of both information and people) between industry, regulatory agencies and research institutions are more prevalent in the US. Consequently, regulators have a better appreciation of how industry works, and are better placed to discuss the scientific basis of their data requirements and the interpretation of results.

These participants felt that Canada could benefit from a higher level of interchange, not least to overcome some tendencies among regulators to be disdainful of industry researchers and yet to feel at a knowledge disadvantage when dealing with the public research community. (This was not a general conclusion consistently made by all industry commentators and nor did they apply it to all Canadian regulatory groups.)

7. US regulatory framework is more politicized, but is also more publicly accountable

The US regulatory framework is more politicized than in Canada, leading to delays in approvals for commercial use of biotechnology products. While rbST is probably the best known example of how actions by special interest groups or at the political level can delay regulatory approvals, other examples do exist. Two possible reasons may explain this difference between the two countries:

- Regulatory agencies in the US have been subject to a high degree of congressional and public oversight flowing from the more intensive level of public debate over the benefits and impacts of biotechnology.

- Senior executive positions in US regulatory agencies are more politicized than in the Canadian government, and appointees add another element of personal judgement, or bias, to the process, or the timeframe, for reviewing and approving biotechnology products.

8. Public awareness and acceptance activity needs to be factored into companies' regulatory planning

Reactions to the commercial introduction of genetically engineered products, such as rbST and *FlavrSavr*™ tomatoes, have moved the acceptance of biotechnology products up the public agenda in both Canada and the US. The pending introduction of a range of other biotechnology products that, on the surface, appear to pose significant risks and/or dubious benefits will add to the issue of public acceptance. (For example, recent publicity on herbicide-resistant seeds has made selective use of information to suggest that the products are "toxic" under the requirements of CEPA.)

The lesson for companies intending to submit products for regulatory approval is that priority has to be given to building public awareness and acceptance. This need is greatest when the biotechnology products in question benefit primary producers with minimal direct benefits for end-use consumers.

The general theme that appears to run through these findings from our case studies (which, it must be recognized, represent a limited sample base) is that Canada:

- Has established a regulatory framework that, for agri-food biotechnology products at least, could prove to be very effective. Biotechnology products falling under CEPA will be assessed using a risk-based approach, but one which appears to be based on zero-risk tolerance.

- Requires a higher level of detail (more extensive data, more field trials) than the equivalent US regulatory agencies to support product submissions.

- Has built the potential for flexibility into its regulatory system but has not demonstrated how this flexibility will be applied.

- Could be put at a competitive disadvantage because of the costs involved in obtaining product approvals in Canada, compared to the US.

In turn, this final point could mean that companies choose not to invest in production in Canada, not to import otherwise beneficial biotechnology products, or seek product approvals outside of Canada and focus their production and marketing efforts outside of Canada. This conclusion runs counter to the view expressed in some Canadian government quarters that strict regulatory standards can be used to stimulate R&D and innovation. This may be true in well-established industries where Canada is a major player, but is less applicable when Canada is a minor player in a highly globalized and competitive industry. The above conclusions also suggest that Canada is falling short on one of our guiding principles for regulating biotechnology; to: "Foster a favorable climate for development, accelerating innovation and adoption of sustainable Canadian biotechnology products and processes".

V

Understanding American Regulatory Advantage

The regulatory framework and the constituent enacted laws and regulations do not reveal any apparent reasons for the perceived superiority of the American system. Other factors explain why industry perceives that the American system offers advantages to those seeking approvals.

The relationship between regulations, policy and public confidence provide some insights into these other factors that have contributed to a capacity for relatively efficient review and thus supportive of commercialization. Events in the public domain appear to have contributed to a supportive environment based on public confidence.

A. Scientific consensus provides basis for product-based regulatory oversight

The application of a product-based approach to regulation depends on the scientific assumptions that underlie it. Specifically, are the techniques of the new biotechnology sufficiently novel to elicit a new regulatory paradigm? The compelling argument against new regulations is predicated upon the following:

- Considerable experience with the planned introduction of traditional genetically modified organisms has demonstrated that risks are understood, evaluable, and manageable.

- Existing regulatory mechanisms have generally protected human health and the environment, while permitting industrial innovation.

- There is no evidence, either theoretical or experimental, that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms.

(This syllogism makes the assumption that conventional biotechnology products have been adequately regulated—an assumption that may be open to question. What seems incontrovertible, however, is that no rationale has been offered for a disparity of regulatory oversight, between new and conventional biotechnology products—particularly if it is the more precise, state of the art techniques that are subject to more stringent regulation.)

The scientific community has endorsed such a point of view in a series of reports and statements (see Exhibit V-1).

Exhibit V-1
Scientific consensus supports a product-based approach to regulation

■ **Risk is inherent in the nature of the product and the environment, not process. . .**

- ICSU Scientific Committee on problems of the Environment (SCOPE) and the Committee on Genetic Experimentation (Italy, 1987)
  - "It is the organism itself, not how it was constructed, that is important"
- Report of a NATO Advanced Research Workshop (1987)
  - "...identification and assessment of the risk of possible adverse outcomes should be based on the nature of the organism and of the environment into which it is introduced, and not on the method (if any) of genetic modification"
- UNIDO/WHO/UNEP Working Group in Biotechnology Safety (Paris, 1987)
  - "...the level of risk assessment selected for particular organisms should be based on the nature of the organism and the environment into which it is introduced..."
- US National Academy of Sciences Policy Statement (1987)
  - "The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods...the assessment of risks...should be based on the nature of the organism and of the environment..."
- US National Research Council (1989)
  - No conceptual distinction exists between genetic modification of plants and organisms by classical methods or by molecular techniques that modify DNA and transfer genes"

B. Myths undermine application of regulations

Notwithstanding scientific consensus, several myths have emerged about biotechnology that are shaping regulations and their application. Our interviews would indicate that these are indeed myths which can be put to rest. The myths appear to have been popularized by either the research community to attract more funding (Myths 1&2) or by public activists to further their causes (Myths 3 through 6). The following discussions seek to cast doubts on all of the myths and are based upon the recent work of team member Henry Miller. More open debate on all of the following myths would contribute greatly to the appropriate application of regulatory oversight.

1. New applications of a discrete technology

Biotechnology has become a 'catch all' term for a broad group of useful, enabling technologies with wide and diverse applications in both industry and commerce. A useful working definition such as 'the application of biological systems and organisms to technical and industrial processes' raises doubts on the validity of the assertion that biotechnology is a discrete new technology. The definition encompasses processes as different as fish farming, forestry, the development of disease-resistant crop plants, the

production of enzymes for laundry detergents and the genetic engineering of bacteria to clean up oil spills, kill insect larvae or produce insulin. Biotechnology encompasses a myriad of dissimilar applications. Without systematic, uniform characteristics, it cannot be effectively legislated or overseen in a uniform, all-inclusive manner that is possible in other industries.

2. Biotechnology and genetic engineering are new

Ancient forms of biotechnology have been recited in other studies—brewing of beer, guided mating of animals and crop plants. Traditional genetic engineering, the indirect manipulation of an organism's genes by the guided mating of animals and crop plants to enhance desired characteristics, has also been practiced for thousands of years. The new technologies enable genetic material to be modified at the cellular and molecular levels, yielding more precise and deliberate variants of genetic engineering, thus producing better characterized and more predictable results while retaining the aims of classical domestication. Building on the domestication of microorganisms for the modification of foods, industry has used the techniques to yield many valuable organisms (the genetic improvement of yields of penicillin, for example).

Planned introductions of organisms into the environment, including insects, bacteria, and viruses have also successfully been used to control weeds, nematodes, insects and diseases such as parotitis, rubeola, rubella, poliomyelitis and yellow fever in various part of the world for many years. What is new are some of the molecular techniques for genetic manipulation. However, in the case of plant, animal and human applications, the techniques, including recombinant DNA, are providing more precise, better understood and more predictable methods for manipulating genetic material.

3. The unknowns outweigh the knowns

What appears to be important from a regulatory perspective is to determine what knowledge gaps have bearing on safety, efficacy or the environment. Numerous microorganisms of beneficial, commercial interest including the microbes used in fermentation are largely uncharacterized. Until recently, field trials of native or non-pathogenic microbes modified by classical techniques were exempt from regulatory oversight and can demonstrate long safety records.

4. Novel and dangerous organisms will be created

Introduction of foreign genes into a plant or animal genome does not create a new organism. Bacteria have long been exposed to DNA from disintegrating mammalian cells (infected wounds, for example). To assess the likelihood of new and dangerous organisms being created, one might consider the potential number of mammalian-bacteria hybrids that are likely to have appeared, been tested and discarded by natural selection over the past millions of years. Genetic and ecological constraints operate to prevent the emergence of exceedingly pathogenic viral variants. While the variations that continually occur on a large scale in nature occasionally produce a modified pathogen, such as influenza or the AIDS virus, it is hardly likely that they would produce in one fell swoop a serious pathogen from a non-pathogen.

Furthermore, the chances of such an event arising from the small scale changes made by man do not compare with the tremendous background 'noise' of recombination and natural selection in nature.

5. Non-pathogens will be transformed into pathogens

Pathogenicity requires the evolution of a special set of properties that involve a number of genes whose functions control factors such as fitness, virulence and adhesion. A pathogen must possess three general characteristics, which themselves are multi-factorial: 1) it must be able to metabolize and multiply in or upon host tissues; 2) it must be able to resist or avoid the host's defence mechanisms for a period of time sufficient to reach the numbers required to produce the disease; and 3) a successful pathogen must be able to survive and be disseminated to new host organisms. The probability of inadvertently creating an organism capable of producing a medical or agricultural catastrophe is small.

6. All technology is intrinsically dangerous

The basis of such a belief may lie in a fear of disturbing the natural order combined with unfamiliarity with the statistical aspects of risk. While examples of toxic spills and nuclear disasters are often cited as the basis for fears, the benefits of telecommunications, vaccinations, microchip circuitry and improved productivity of plants and animals are often passed over. Application of regulatory oversight exists to ensure that safety against potential harmful effects is maintained.

C. Role of industry is well articulated in the US—not so, in Canada

The biotechnology industry has grown at a more rapid pace and is on a more significant scale than the Canadian industry. There are numerous studies and other evidence to substantiate this observation. Two important conclusions may be drawn from this situation:

- The health of the US industry may be attributed to some extent to the ability to develop and commercialize products within a supportive regulatory system.

- The size of the industry and its ability to speak authoritatively have had an effect on the evolution of the regulatory framework.

American industry educates the public, critiques and responds to government regulatory proposals, and lobbies government to provide support. The industry, even in formative years, was able to influence the policies of the regulatory agencies through presentation of cohesive arguments.

For example, one of the early restraints on commercial growth was the overly restrictive USDA regulations on importation of cell lines because of concerns about foot-and-mouth disease. An industry-sponsored study conducted by the Association of Biotechnology

Companies addressed the problem and offered an administrative approach to assuage concerns while facilitating importation. The report was specifically cited in the Coordinated Framework for Regulation of Biotechnology (Federal Register, 51(123):23346, June 26, 1986). The impact of the recommended approach was acknowledged by USDA when a number of revised administrative and technical provisions to expedite importation of organisms and vectors were subsequently instituted.

Specific industry events of note include:

- Development of an ability to counter public assertions and lawsuits by public activists.
- Opposition to EPA proposed regulations which, in turn, were to some extent justified by the example of European regulatory policies.
- Long-term support for product-based regulatory policies.
- Opposition to Biodiversity Treaty constraints on trade and intellectual property.
- Support for user fees to subsidize FDA approval processes for biotechnology and traditional pharmaceuticals.
- Support for importation of biologics and cell lines.

A major difference between the two countries is the relative strength of the three major sectors of application. Canada's biopharmaceutical industry has not been as strong as its American counterpart because of the impact on multinational activity in the country when patent protection was restricted during the 1970's to encourage greater generic drug activity and thus lower costs. The Canadian agricultural sector, on the other hand is well developed with a strong science base and close ties between government and industry.

The influence of industry on government has been significant in the US to the point where the regulatory system has long been oriented to promoting competitiveness. In Canada, the industry is smaller, less able to influence policy and regulations, in part because foreign ownership means many activities take place elsewhere.

D. Champions and their causes

Within the US, there were two groups of "champions"—those favouring the growth of biotechnology within a product-based regulatory policy within existing regulations; and those favouring the growth of government bureaucracies at the expense of R&D, with the implementation of process-based regulations. A concomitant of the latter approach was the assertion that biotechnology was inherently risky (or inherently uncertain) and therefore, required rigorous review with decisions supported by extensive data to prevent untoward surprises.

The most ardent and strident process-based advocates often employed the courts or the threat of court action to thwart introduction of new biotechnology-derived products. The press was another favourite medium for public activists who often employed sensationalism and fear to press home their point of view. The press, in turn, would seek out the opinion of trade associations to counter or clarify the opinions of public activists.

The public debate evolved into a sideshow to the more scientific debate underway in RAC.

The Reagan and Bush White House policies eventually championed and promulgated the product-based point of view, but mid-level agency officials were able to resist the adoption of such policies. Instead, they protected their turf, at best holding out for incremental and minimal changes. At worst, agencies openly contravened official policies.

For example, in the Science and Education part of USDA, Al Young, director of the Office of Agricultural Biotechnology (OAB) attempted to promulgate guidelines regulating a new category of field trials—those with transgenic animals; this attempt was, however, thwarted by the Bush administration because the proposal policy contradicted both scientific consensus and official White House policy. As discussed elsewhere, EPA routinely ignored both scientific consensus and White House policy, sometimes employing the appropriate buzzwords but repeatedly introducing blatantly process-based proposals.

The change of political leadership in the White House in 1993 had the immediate effect of moving policy towards process-based regulation. Under Vice President Al Gore and Chief Domestic Policy Advisor, Greg Simon, expectations were that regulatory oversight would increase, review requirements would dramatically rise, and that rDNA-focused regulation would be born-again. Events have, in fact, largely borne out these expectations.

While USDA liberalized its biotechnology regulations under the Plant Pest Act in early 1993, the changes were minimal (and watered down from the preliminary proposal published several months earlier, before the change in administration), affecting primarily a few large companies. FDA has drafted (but will probably not now be permitted to publish) a rule that would require notification of rDNA-derived foods (but only those) and placed a number of general (not specifically focused on biotechnology) obstacles in the way of pharmaceutical development; and the regressive EPA regulations under FIFRA and TSCA described above have emerged, some as final rules, some as proposed rules.

Early indications are that changes may indeed be forthcoming, both because of direct Congressional action and because the agencies are scrambling to "reform" in order to head

off externally-mandated changes. The recent Republican congressional election is considered by many of those interviewed by the study team to be a signal that a loosening of regulations is imminent. As a possible harbinger of forecasted change, a package of anti-regulatory legislation that would modify major provisions of most pollution control laws passed in the last 25 years has been introduced to the House in late February, 1995. The approach is indirect, adding additional requirements to existing legislation that effectively renders them unenforceable in many cases. Specifically, the following measures have been proposed:

- National air quality standards must now also adhere to a new cost-benefit standard as well as health considerations.

- Enforcement of the Endangered Species Act's requirement that nobody may harm a protected plant or animal by destroying essential habitat, is to include compensation to private property owners for loss of property market value.

Some of the more prominent champions of the two opposing viewpoints are listed in Exhibit V-2.

Exhibit V-2
Champions and their philosophy

US has had more visible leaders in regulatory development process

Risk-Based Oversight (Innocent Until Proven Guilty)	"Zero Risk" Oversight (Guilty Until Proven Innocent)
US • FDA: Frank Young Henry Miller • White House: John Cohrssen • OSTP: David Kingsbury • Associations (BIO/ABC/IBA): Bruce Mackler Harvey Price	US • EPA: Elizabeth Milewski Donald Clay • USDA: Terry Medley Charles Hess • White House: Greg Simon • Public Activists: Jeremy Rifkin Rebecca Goldberg Margaret Mellon • Associations: Carl Feldbaum
Canada • Western Economic Diversification Janet Smith • AgWest Murray McLaughlin • Saskatchewan Government Roy Romanow • Pharmaceutical Manufacturers Association of Canada (PMAC)/IBAC	Canada • Toronto Food Policy Council • Pure Food Campaign • Environment Canada • National Farmers Union/Council of Canadians

One conclusion drawn from the American experience is that while adverse changes in biotechnology R&D can be ascribed to the Clinton Administration (ranging from decreased research funding and threats of product price controls to additional and more regressive regulation), several factors tend to mitigate such deterioration:

- Biotechnology-derived products and field testing of modified microorganisms over the past fifteen years have demonstrated an envious safety record.

- A growing appreciation of the importance of biotechnology as underpinning international US competitiveness has been instilled in the new Republican Congress.

- Biotechnology as a catalyst for political debate has been largely marginalized. Dire predictions of catastrophe have not been realized, senior advisors within the present administration are no longer at the most senior levels and within agencies, biotechnology is generally being absorbed into more traditional areas.

E. Public confidence

In the American experience, public confidence has been addressed through public debate in the NIH system. Providing public access to the scientific discussions of biotechnology, sponsorship of biotechnology by the Presidency and education by industry has enhanced public confidence.

Public confidence in the value of biotechnology in Canada has been always been considered supportive. However, there are signals that there may be a growing of cynicism and mistrust. Based upon recent events, we are of the opinion that the rising concerns are, in fact, being expressed by public advocacy groups—often for furtherence of their respective causes:

- Recent regulatory failures in the case of breast implants, tainted blood, and falsified cancer test results are increasing the level of public skepticism.

- Recent surveys and focus groups conducted for BIO suggest that there are low levels of knowledge about biotechnology, individuals respond best to accurate, documentable, benefits-oriented information, people respond more favourably to specific anecdotes than general statements about the industry, success stories from patients and consumers are more effective than jargon and people respond well to shared concerns and feelings and a demonstrated sense of social responsibility.

- Recent introductions of products with marginal benefits such as rbST and FlavrSavr™ tomatoes have increased questions about the utility of research innovations.

- Farm organizations are using biotechnology to elevate socio economic concerns about loss of family farms.

VI

Conclusions

A. Features of the American system

1. Comparative advantages of the American regulatory system

From the perspective of an outsider, the American system appears overly complex and confusing. A variety of departments and agencies are involved in regulating deliberate releases, including the US Department of Agriculture, the US Environmental Protection Agency, the National Institutes of Health and States. Involvement of multiple agencies has led to some overlap and regulatory conflict. Regulation is conducted under pre-existing and new health and safety and environmental provisions and involves pieces of existing product-based review schemes and a variety of notification and consent procedures. The system is in a state of flux but, with the new Republican Congress, can be expected to become rationalized and liberalized. Commentators and practitioners have identified for us several comparative advantages of the system despite the above cited drawbacks:

- **Relatively undisruptive** because the system is based on existing legislation—especially for pharmaceuticals and food, much less so for crop plant field testing.

- **Easier and cheaper to perform experiments and obtain consents for release.** For example, the data requirements for microbial pesticides are relatively simple compared to the requirements for an agrochemical—although they are more stringently regulated than non-biotechnology microbials.

- **Reduced prior notice time periods.** For certain key crops the required prior notice of release was reduced from 30 days to 24 hours with only two pages of information on the trial.

- **The vast majority of laboratory rDNA research can be conducted without any system of consents** under the NIH guidelines, except in those cases where federally funded work involves cloning into pathogens, the cloning of a potent vertebrate toxin, and the introduction into a microorganism of new antibiotic resistance (the Recombinant DNA Advisory Committee of the NIH reviews this federally funded work).

- **USDA and EPA do not charge fees.**

In the area of drug oversight, the FDA recognizes the long term health benefits that the use of many biopharmaceuticals drugs can bring—and the importance of this industrial sector. Consequently, the agency is committed to increasing the numbers of staff dedicated to processing requests for notices of compliances for these drugs.

A final important consideration arises when assessing the impact of the American regulatory system on US competitiveness. Beyond the practical advantages, the system is perceived to be less bureaucratic and speedier. Policy statements by the US administration that biotechnology products be considered on their merits as products and not singled out for special treatment because they were genetically modified organisms has undoubtedly reinforced this perception.

A summary of the positive and negative features of the American regulatory regime are provided in Exhibit VI-1.

Exhibit VI-1
Features of the American regulatory regime

+	-
• Not disruptive - existing legislation	• Failure of political will to create a government regulatory policy consensus
• Easy and cheap to perform experiments and obtain consents for release in most cases	• Fluctuation in availability of investment capital
• Most GMO work is conducted without consents (not field trials)	• Some overlap and regulatory conflict
• Entrepreneurial spirit and propensity of scientists and inventors to take risks	• Lack of coordination amongst regulatory agencies
• Product-based oversight (in theory)	• Introduction of new technique - specific regulations
• Champions have made significant improvements	• Agricultural and environmental sectors appear to be "underperforming" under rigid regulations: -R&D only at moderately high levels -Investor interest low
• Intellectual property protection	

B. Similarities and differences

While there are many key similarities, the American system has a stronger scientific base, a more robust industry, a larger domestic market and more visible political leadership. Canada has advantages in two key areas—regulations are less complex and a collegial political

system facilitates co-operative effort. A summary of similarities and differences is provided in Exhibit VI-2.

Exhibit VI-2
Similarities and differences between the American and Canadian regulatory regimes

Similarities	Differences
• Legislation • Philosophies and principles • Agencies and their jurisdictions • Maturity of regulated domains • General evolutionary path • Many common industry players	• Supportive government attitude/leadership in the US • Complexity of regulations in US* • Substantial research base (US) • Larger industrial sectors (US) • Greater public participation and a higher profile (US) • Voluntary registration and notification is well developed in US • Collegial (Canada)* vs adversarial (US) political systems • Expectation of a diminished role for government in US • High degree of movement between industry, government and academia in US structure • Naturally occurring organisms (CEPA) are at federal (Canada) vs. State level (US) • Novel foods—regulated (in Canada) vs. a statement of policy (US)

** Canadian advantages.*

C. Impacts of over-regulation

Several examples have been identified that illustrate the detrimental effects of over-regulation (see Exhibit VI-3).

Exhibit VI-3
Examples of the effects of over-regulation—US

Over-regulation has a detrimental impact on industrial growth

Performance Indicator	Regulatory Climate
• Share prices for biopharmaceutical firms outperformed the market by 200% between 1983-1992	• FDA adopted a scientifically reasoned policy • Regulate bioproducts no differently than others • Approved 20 drugs/biologics in less than approval times • Permitted 1,500+ clinical trials
• Share prices for agricultural biotechnology firms underperformed the market by 20% (despite major breakthroughs in basic science)	• Field testing of new biocontrol and other products faced additional regulatory requirements because used rDNA techniques • Regulatory and judicial delays
• 10% of researchers in public sector and 20% of researchers in private sector who had developed new organisms related to agriculture elected not to proceed with field trials—3/4 citing reasons related to government regulation*	

** No baseline for comparison. Based on a 1989 survey (Ratner—Bio/Technology 8, 196-198).*

Detrimental impacts of excessive regulation can be further illustrated with international examples:

- Japan has a process-based regulatory philosophy and has enacted strict regulations in foods and food additives—even with a sophisticated scientific infrastructure, Japan is not close to introducing any products into clinical trials, not a single company has been created with gene therapy as its goal, only three field trials of rDNA-manipulated plants have been carried out and R&D is far behind other countries.

- Denmark, Germany and the European Union have created regulatory disincentives for the use of biotechnologies—Denmark's Novo/Nordisk Industry, the world's largest producer of enzymes, has threatened to move to Japan and German companies have aggressively re-located R&D operations abroad.

D. The limitations of regulation

For thousands of years, humans have been selecting, sowing, and harvesting seeds that produce food products. They have also been making bread, brewing beer and making wine and cheese. Although they didn't understand the genetic science involved, early farmers, ranchers, bakers, brewers and vintners have been harnessing biology for centuries to make and modify plants and food products.

Our ancestors moved and changed genes through intensive breeding to enhance the beneficial qualities of food. Modern technology allows food producers to do the same things today but with greater understanding and selectivity.

The ability to directly read and alter the genetic code may be one of the most significant discoveries in the evolution of biology. The possibilities of this new biology are almost endless—the natural world has become malleable.

The scientific and legal basis of the current regulatory systems in place controlling the applications of biotechnology have essentially been outpaced by the technology itself. We are witnessing the maturing of the science—the issue is how we should behave in a world in which biological information can be manipulated:

> *" The power of the gene has been revealed as partial and couteractable: the awesome biological power of humanity is still only embryonic. This interregnum is a good time to start making decisions about how to best effect the handover of power from nature to man. Those decisions will be difficult. But the general principles to help and guide them can be identified now: respect for autonomy, respect for variety, respect for equality.*
>
> *To think of genes is to think of generations: of the birth of a child in whom the old has been made young again, and which will, in time, grow to adulthood itself. Who can say when that transition is made, and the child becomes and adult? Perhaps it is when it can itself give birth; perhaps it is when it can see its parents for what they truly are. On either count, humanity is coming to the end of its childhood. We are seeing the world that is created for us for what it is. We are within the reach of the power to create it anew. It is a moment of joy; and for fear, and, most of all for responsibility."* [2]

A key to regulatory evolution is responsibility on the part of both the industry and the regulators responsible for human and environmental safety. The biotechnology industry cannot expect to work in a totally unregulated environment. However, at the same time the regulators must recognize the limitations on their knowledge and the cumbersome procedures that accompany most regulatory systems. It is encumbent on regulators to work with industry so that the innovation and genius associated with this new technology has maximum opportunity to grow, prosper and provide products that benefit the economy, society and the consumer.

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[2] *The Economist, February 25th, 1995.*

VII

Applying Lessons From The American Experience

A. Canadian issues

This study has shown how Canada potentially has a regulatory system comparable to the best in the world. However, we have also found the thrust to complete the necessary adjustments to make the system more efficient is lacking. In this vacuum, aggressive public activism and political maneuvering could unduly influence the regulatory process and policy development. While regulations have become a focal point, several other factors are also of concern.

1. Exponential growth in regulatory issues

Several surveys of Canadian biotechnology companies have found that the most cited issue facing companies is the complexity of Canada's regulatory environment. Even though the principles for regulating the assessment of many biotechnology products have been established, the actual promulgation and implementation of regulations and guidelines—and the provision of suitable resources within regulatory agencies and establishment of operating principles—is an area of great concern. Specific challenges include:

- Formalization of regulatory structures for biotechnology products, especially those applying to biotechnology products in the ag-food and environmental industries.
- The parameters used by the Patent Medicine Prices Review Board to evaluate pricing of patented drug products, which, increasingly, are produced through the application of biotechnology and appear, on the surface, to carry high prices.
- The emerging area of pharmacoeconomics.
- The intent of the Health Protection Branch to impose significant fees for drug submissions without corresponding commitments to investing in resources to expedite processing of applications.

2. Product approvals and market entry

An increasing number of companies will be facing the challenge of managing, and funding, the movement of their products through the regulatory approvals process and onto the market, both in Canada and internationally. Currently, the industry is concerned with the time required for regulatory review and for the processing of patent applications.

3. Emerging aversion to risk and societal re–evaluation of paradigms

As indicated earlier in this report there is a growing aversion to risk within society. This aversion has come about as a result of infrequently occurring but highly publicized results of regulatory failures resulting in the expression that present safeguards may not be adequate.

Groups that purport to be acting on behalf of consumers are asking "what's in it for me", and demanding that the benefits of a product must be clearly demonstrated before they should be asked to take a risk. These types of questions are being asked particularly in the agriculture and food sector and less frequently in the pharmaceutical/medical sector. People question less the origins of a pharmaceutical that will save their life or improve their quality of life. When contemplating food, however, they will say "we already have enough why do we need to change the way things are done now to produce more?"

Increased and instantaneous access to information has also lead to increased access to misinformation which has aided in heightening concern. It has also lead to people asking "who do we believe, who do we turn to for accurate information?" Signs of societal questioning of existing paradigms to define "success" and "progress" are growing and exemplified in the suggestion that our existing health and safety regulations should use more than scientific criteria to evaluate a product, and that societal issues should be considered.

4. Restricted sources of capital

Commercialization of biotechnology products is an expensive process, requiring frequent infusions of capital and a willingness by investors to assume both financial risk and a long term view to receiving a suitable risk-adjusted return on their investments. While the financial environment has improved—in terms of an improvement in the willingness of venture capitalists and institutional funding sources to invest in Canadian biotechnology companies—it still lags behind the US market.

5. Anticipated rise in volume of applications

Questions are being asked as to whether there is a critical mass of current scientific expertise in the Canadian regulatory system to evaluate the ever increasing number of applications from companies sponsoring products for registration. The private sector is concerned by the number of evaluators and their expertise and the backlogs that are

resulting.

6. Limited resources to apply regulations

Dramatic cost cutting initiatives across the federal and provincial governments are placing severe constraints on the ability of regulators to review applications. Agencies have three general approaches available to them: tighten regulations and the requirements for approval to restrict the number of applications; increase the number of reviewers by adopting user pay schemes as has been adopted in the US; or apply a product-based risk assessment approach supported by scientifically-defensible evidence.

7. Increasing need to interact with multiple levels of government

Federal approvals of biotechnology do not ensure market access in Canada (nor in other countries, such as the US). Once safety and efficacy concerns have been dealt with, it is often necessary to deal with issues related to actual product use, which typically fall under the jurisdiction of provincial and municipal jurisdictions.

8. Access to/availability of skilled research and production people in Canada

The commercial production, marketing of biotechnology products and the management of regulatory affairs requires a different mix of skills and capabilities than those associated with the initial R&D processes. The development and supply of such skills is becoming increasingly important to the sector, as it is to educational and research institutions.

9. Fragmentation of advocacy and government relations efforts

There are many different organizations that represent the interests of biotechnology companies and research organizations. There is a bewildering array of organizations that, legitimately, represent various interests in the biotechnology sector, especially for people and organizations that are not familiar with the structure nor complexity of the sector, including elected representatives in provincial and federal Parliaments. However, only one organization—IBAC—has a mandate to provide a national voice on behalf of the interests of commercial biotechnology. The key issue is to find ways of combining the interests and resources of these groups for the common benefit of each jurisdiction. The risk is that the best-intended efforts may be fragmented and fail to achieve a suitable "critical mass". Moreover, what is best for one stakeholder, such as industry, may be anathema to another, such as academia.

B. Underlying factors

1. Pervasiveness of myths

Regardless of their origins, the biotechnology public myth in Canada could be summarized as:

> *Biotechnology is genetic engineering; it is so new we really don't have a grasp on all possible things that could happen. Since all technology is intrinsically dangerous it is probable that dangerous and uncontrollable products will result.*

The other biotechnology myth in Canada, held by the private sector, is that the US regulatory system is "so much better than ours and that ours makes us less competitive." Our comparison indicates that we have similar systems and that Canada is poised to have a better system if we do not get bogged down in politicizing the regulatory process. ***The essential difference between the US and Canadian experience is that there has been more articulated leadership demonstrated by politicians and private sector biotechnology industry associations in the US.*** The public debate in the US was wholeheartedly engaged years ahead of the commercialization of products.

Until the Canadian Government and the private industrial sector address the second myth and then wholeheartedly engage in open public debate and set in place initiatives to address the first set of myths our regulatory system is in jeopardy of becoming even more politicized. Instead of building on an opportunity at this point to create the most efficient regulatory system in the world, we could allow it to become truly uncompetitive.

2. Small domestic market

Because of the small size of the Canadian market, transnationals are reevaluating whether the Canadian marketplace justifies the effort and costs associated with seeking a Canadian regulatory registration.

Canadian based (and often cash strapped companies), are asking themselves if they only have the financial resources to sponsor an application to one regulatory process, "is Canada the best place to get the biggest bang for their limited buck?"

3. Rising politicization of biotechnology and the regulatory process

In the absence of a clear message that biotechnology is important to the future economic well being of Canada the issue will become more politicized resulting in regulators being reluctant to make decisions. "You get into less trouble for not making decisions than for making decisions that get politically hot." Regulators can not be totally faulted for taking this approach as they can watch on TV or read in national newspapers that someone is looking over their shoulder. Special interest groups are

using biotechnology and societal issues as a rallying point to revive their ailing organizations, with the intention of bringing attention to their main agendas, as witnessed very recently by the debate initiated by biotechnology opponents on the front page of The Globe and Mail or on CTV's Canada AM.

Departments of the Canadian government may also be seen to have politicized biotechnology for their own ends. Witness the debate over who has lead regulatory roles such as which department should have the authority to conduct/oversee environmental safety assessments.

4. Intellectual property rights

Business viability is derived from the ability to recoup research investment through exclusivity of product offering—hence, competitive advantage. Inability to protect intellectual property in Canada reduces the rationale for seeking regulatory approval in Canada, especially when market size is also factored into business planning. Canada's approach to the patentability of higher lifeforms is markedly different from that of the United States and other OECD countries, such as Australia. While Europe has yet to come to a formal adoption of patentability, the US Supreme Court established patentability of life forms through *Diamond vs. Chakrabarty* in 1980.

C. Horizontal themes

1. Political will and a logical system

The evolution of a logical and predictable regulatory system does not in, and of itself, ensure that industrial interests are served. The American experience indicates that strong political leadership speeds up review. In fact, one criteria used to evaluate the quality of an investment is whether the government/political process is supportive. Political support has yet to find a strong and consistent articulation in Canada—certainly political support for the sector has not been consistent in Canada with the exception of some provincial jurisdictions.

2. Public trust and risk assessment

Acceptance of product-based risk assessment, a major contributor to efficient regulation, is largely dependent upon the degree of public confidence. In our analysis, confidence springs to a great degree from the exposure and de-bunking of popular myths about the possible detrimental aspects of biotechnology.

3. Profile and communications

An indirect benefit of the public review process and the open debates that have often been prompted by biotechnology is the elevated profile of biotechnology. The contributions of science and industry to the debate have been the articulation of benefits to society and to the economy.

4. Equivalency and reciprocity

While Canada has a friendly environment for conducting research, it must also provide a commercial and regulatory environment that enables product approvals in Canada to be recognized elsewhere. To do so requires that *final-product standards* be consistent with those of Canada's trading partners, and that regulatory approvals proceed in a timely fashion. (It is important to note that the stringency of Canadian regulation whose purpose is to ensure product safety and/or efficiency—for example, for foods and pharmaceuticals—is appropriately relevant to our trading partners. However, regulation pertaining to the safety of the workplace or the environment—such as the regulation of the field testing of plants—is irrelevant to the acceptability of Canadian products in importing nations. Importing nations' considering such factors could be construed as the erection of non-tariff trade barriers, although such factors are sometimes used as a specious argument for a higher level of domestic regulation.) In fact, if Canada were to adopt more rational, risk-based, and transparent regulations than its trading partners, it could well become a haven for biotechnology product testing and commercialization).

An important element of harmonization is insistence on reciprocity, thus capitalizing on areas of recognized strength.

5. Predictability of timeframe

Capital flows to places where it feels that it is welcomed, and where it can make a return. Return on an investment is in many regards predicated on the time that it takes a product to get to market. This time to market is often affected by the length of time that it takes the regulatory system to evaluate the product. Without a clear understanding of the regulatory evaluation time frame investors are less likely to invest. This is often expressed as a need to have a predictable regulatory process, not necessarily where the answer to all applications is yes, but one where the steps and the time frames of the application are fully understood at the beginning of the process.

D. Adopting the best American features

Our review of the American experience suggests several features that have contributed to an environment supportive of enterprise. We suggest that the differences between the two systems lies not in the regulations but in the following factors which should be considered for adoption within Canada:

- Reliance on scientific principles as the basis for regulatory policy.
- Strengthening of leadership for biotechnology to raise profile.
- Intellectual property protection.
- Public involvement where it involves comment and education.

- Scientific debate to instill and/or reinforce responsibility.
- Integration of the stakeholders to strengthen influence in the political and regulatory domains.

VIII

Recommendations

If Canada is to benefit from the lessons learned south of the border, we should strive for greater balance between regulators and industry with the concurrence of the Canadian public. To enable Canada to emerge as a leader in the biotechnology-related areas in which we excel (agriculture, health care niches, and environmental science), a series of initiatives to foster leadership, enhance science literacy and encourage regulatory equivalency are recommended. Strengthening the influence of industry, improving access to scientific information and experience, bolstering public confidence and encouraging the adoption of best regulatory practices will create an appropriate climate for efficiency in application of regulations—a stimulus for commercialization.

A. Foster leadership

The Minister of Industry is well positioned to play a leadership role in facilitating coherency within industry groups and development of a strong, unified 'voice'. ***The Minister of Industry should facilitate a forum for interested associations and industry representatives to design the framework for a coalition around a pivotal association to provide a unified industry voice.***

The primary national trade association representing Canadian biotechnology companies is the Industrial Biotechnology Association of Canada (IBAC). This association is too underfunded and understaffed to address the broad span of regulatory agencies and the public's need for information. Unfortunately, its resources are limited because many of IBAC's members have not yet or are just beginning to turn a profit. Many more established trade associations have a secondary interest in the issues of biotechnology.

Stronger linkages between IBAC and established associations will provide a basis for an issues coalition focused on biotechnology and public and environmental safety.

Because of the magnitude of the task and the importance for Canada's future economic well being industry, with the encouragement of the Canadian government, should increase resources to IBAC and foster linkages with associations that are related to the biotechnology sector.

A rising profile and industry leadership will provide sufficient catalyst for the emergence of appropriate political leadership. A myriad of issues and challenges dictate that now is an appropriate time for a political champion and support for the biotechnology sector in Canada. The need is for consistent articulation that Canada is supportive of the biotechnology sector—it is necessary to encourage such leadership to come forth.

Industry is fragile in this country and would benefit from the encouragement of the Canadian government. The Minister of Industry should extend a strong invitation to industry to participate in a consensus-building discussion using the occasion to send several messages:

- To the Canadian public and investor in the sector, that the Canadian Government is supportive of biotechnology research and commercialization , that appropriate safeguards are in place to assure safety of products and that this technology is advantageous for Canada's future economic well being;

- To Canadian regulators, to concentrate on regulating products using scientific principles and processes and to leave the possible political sensitivities to the political process.

B. Promote best practices to capitalize on the potential flexibility of the Canadian regulatory framework

Further development of the Canadian regulatory framework should aim to capitalize on the potential flexibility inherent in the structure of Canada's regulatory requirements. In doing so, the opportunity also exists to learn from, and apply, lessons from the US experience. For example, the US Food and Drug Administration, responding to a broad coalition of concerned stakeholders, is likely to undergo reform, perhaps significant reform, which will accelerate and improve the approval processes. Specific measures adopted or under review include focusing more on reviewing only those applications perceived to be riskier, charging user fees to increase resources for review, and exemption and expediting reviews of applications where there is perceived low risk based upon previous experience. To date, no comparable moves have occurred in Canada.

The Minister of Industry should contribute to improving regulatory efficiency by promoting superior regulatory policies amongst regulators. In particular:

- Ensure that regulation is only that amount which is necessary and sufficient. This means ensuring that Canada's commitment to applying risk-based product-focused regulatory principles is observed at the operational level, and establishing mechanisms to re-assess data requirements in the light of advances in scientific knowledge and product familiarity.

- Capitalize on the potential flexibility by Canadian approaches, while building in appropriate checks and balances to ensure transparency and predictability. The checks and balances should include mechanisms to ensure that: any problems regarding data requirements and data interpretation are resolved; and, that reviews are conducted objectively and consistently.

- Encourage regulatory agencies to use external scientific review panels, and establish policies to determine:

  - When a product should be referred to an external panel, or when a

company or an agency can request an external review.

- The way(s) regulatory agencies can respond to panel recommendations.
- The timeframe for reviews and responses from regulatory agencies.
- When a product or a manufacturing process need not be subject to regulation.

- Encourage regulatory agencies to improve their accessibility and responsiveness to companies making submissions and seeking product approvals. The review process should provide opportunities to establish bi-directional, professional working relationships between agency reviewers and companies' product development and regulatory specialists, for the purposes of determining potential product risks, solving problems that arise during the review process, and obtaining feedback on progress.

- Encourage regulatory agencies to increase the resources available to meet anticipated future workload and knowledge requirements. The merits of user fees should be evaluated and, if appropriate, used to fund the additional resources.

- Leapfrog the shortcomings in the US regulatory system where it overregulates and creates disincentives to the new biotechnology (e.g., overregulation of field trials by EPA and USDA/APHIS; duplicative regulation of gene therapy by IBCs, NIH, IRBs, FDA, etc.).

- Emphasize regulatory notifications and "hammers" ("drop dead deadlines") in Canadian regulation.

- De-emphasize case-by-case government reviews, except where absolutely necessary.

- Do not subject products of the new biotechnology to regulatory requirements or procedures in excess of those for other products, without a clear scientific rationale.

C. Accelerate application of equivalency and reciprocity

Once our regulatory system has evolved, ***Canada should move rapidly to develop with other nations agreements that establish final-product quality standards so as to promote equivalency and minimize duplication of regulation.*** We are presently in a position to have the most scientifically-based and progressive system in the world to evaluate products of biotechnology. With these agreements and the recognition of the status of our regulatory system, Canada could use this to its competitive advantage. This would not only become an export service sold to other countries but would also attract companies to come to

Canada to conduct research and development and commercialization. This approach could be the subject of several test cases focused on a product/regulatory area where we already have a high international regulatory expertise standing.

NBAC should play a proactive role in putting in place such agreements with other countries. Within the domain of agriculture, for example, Canada is in a position to work with an industrial partner, AAFC and USDA to establish an acceptable approach to development based on a defined common philosophy and guiding principles. Once a pattern has been crafted, other agencies could work under an umbrella interdepartmental committee to identify regulatory centres in areas of strength that could logically contribute to reciprocal arrangements.

Promotion to regulatory agencies of greater acceptance of the results of international science and conscious expansion of access will strengthen the initiative.

D. Encourage harmonization of federal and provincial regulations

Several recent initiatives to encourage greater harmonization between federal and provincial regulations as well as amongst the regulating agencies have been underway over the past one or two years. While the Minister of Industry is not directly involved in such efforts, continual encouragement by the Minister on behalf of industry will create a sense of accomplishment and thus, contribute to continuous improvement of the regulatory framework.

E. Enhance understanding of Canadian biotechnology policies

To address the public's lack of scientific understanding about biotechnology and its benefits, an overall supportive communications and education strategy involving the government and the private sector needs to be undertaken. ***Cornerstones of this initiative should include the establishment of a "Blue Ribbon" panel of scientists and public policy experts to discuss the science underlying biotechnology processes and related issues, including regulation. The results of this panel will need to be widely publicized.***

In addition, a supportive communication and education strategy should be designed and implemented. Integral to this strategy would be a conference designed to address socio–economic issues and to articulate the benefits of biotechnology, on the theme "Biotechnology and the Public Good". The results of this conference will need to be widely publicized. Several essential elements for this public policy discussion would include:

- Elaborate, elucidate, but don't permit misapprehensions to determine or alter policy.

- Present as a *given*, and *explain*, but do not debate, the scientific consensus over new biotechnology—that there is no conceptual distinction between altering the

genetic make-up of organisms by conventional techniques and by genetic engineering; and that new biotechnology is essentially an extension or refinement of earlier techniques.

- Explain that products that seem arcane and even threatening are, in fact, often indistinguishable from those that are mundane, familiar, and even essential to every-day life. Examples of the former include cheese made from recombinant chymosin and *FlavrSavr*™ tomatoes; of the latter, yogurt, common foods derived from wide crosses in plants across natural breeding barriers, vaccines, enzymes in laundry detergents, beer, etc.

A longer term initiative of the Minister of Industry that would contribute significantly to public understanding is development and diffusion of factual information about biotechnology to Canadian schools.