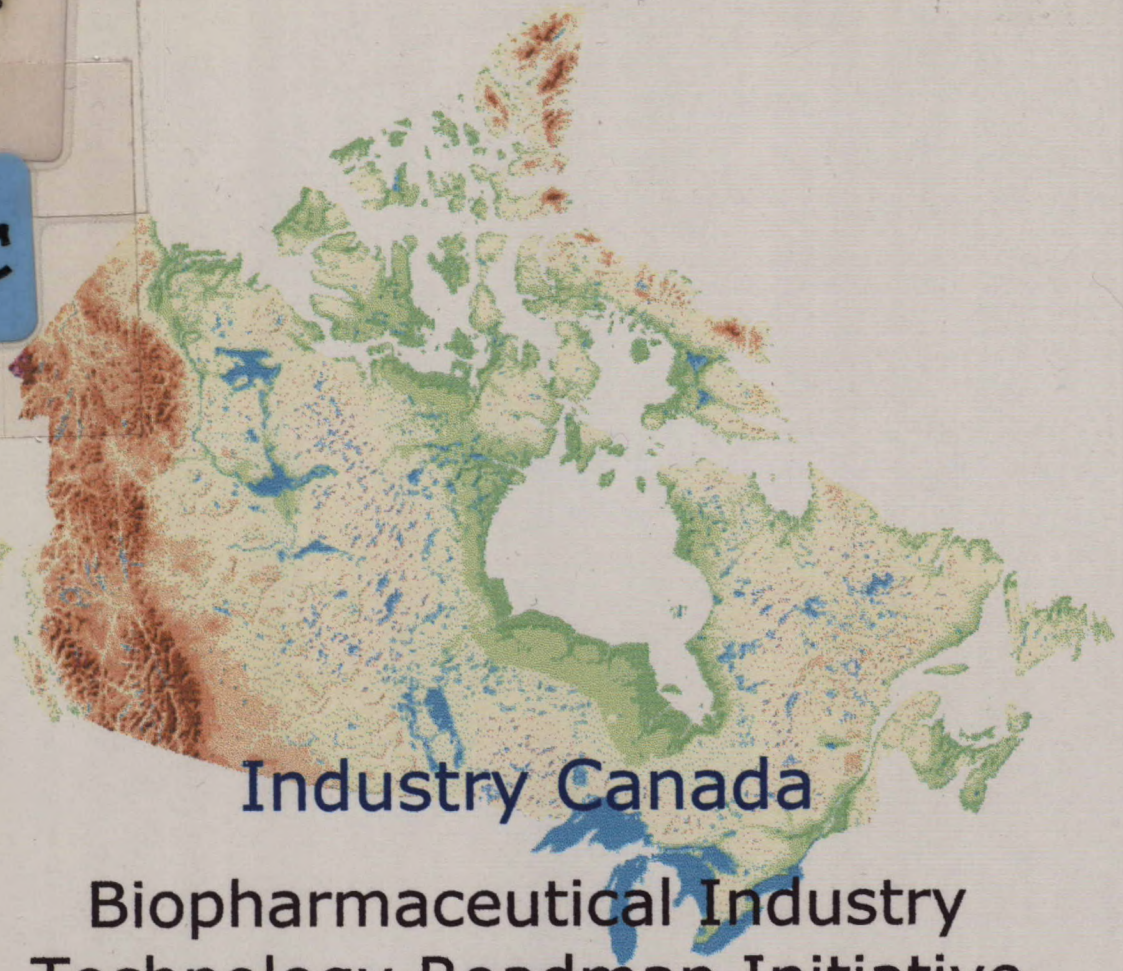

Industry Canada

Biopharmaceutical Industry Technology Roadmap Initiative Preliminary Work

Volume 1: Report

May 1, 2000

strategic health innovations

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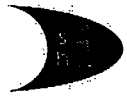


Executive Summary

Abstract

Prior to Industry Canada's launch of a Technology Roadmap (TRM) Initiative in the biopharmaceutical industry, STRATEGIC HEALTH INNOVATIONS was commissioned to perform background research, consultations with a sampling of key stakeholders, an analysis of key findings and make recommendations regarding the approach to the TRM. From across Canada, executives in biopharmaceutical companies and academic research leaders were asked about their perspectives on the technological strengths, weaknesses, opportunities and gaps in the industry and their interest in participating in an industry-led, government facilitated TRM.

Globally, the biopharmaceutical industry is experiencing explosive growth as basic researchers generate new biological molecular entities that will form the bases for new drugs. In Canada, the development of this innovative research takes place in many small companies that take the technology from the laboratory through to the stages of applied research, pre-clinical and clinical trials. The outcome of success is very significant global revenues for new drugs and possible cures for major diseases.

Large pharmaceutical firms that are chemically based have not been very successful at the innovative stage of biological and genomics research and have been forced to establish alliances with smaller biotech firms. The value of these alliances was over $2 billion in 1998 and expected to increase as many new biological based drugs enter the market.

The Canadian biopharmaceutical industry is still quite young but is already ranked second in size behind the U.S. and has a very impressive rate of new company creation. It is also an industry that has to compete diligently for capital, management and strategic alliances. Canadian biopharmaceutical companies have developed great strengths and resourcefulness and are much more competitive against other international companies than they may realize. The continued success of this industry, however, is dependent on the quality and volume of basic research in technologies.

Introduction to the Technology Roadmap

Definition

A **Technology Roadmap** is a practical business forecasting tool that gives firms in a given sector a way to predict their future technology and product needs, and map out how best to attain them. By involving industry, research, government and other relevant stakeholders, it can substantially influence the focus of research and development efforts, as well as strategies, policies and programs of stakeholders. By providing better technology planning, a Technology

Roadmap can be a key instrument for guiding the growth and international competitiveness of the Canadian biopharmaceutical industry into the 21st century.

Methodology

STRATEGIC HEALTH INNOVATIONS consulted 42 industry executives and academic leaders of the biopharmaceutical industry in Canada during March 2000. The overall response from members of the biotechnology and pharmaceutical industries was extremely positive. Participants were selected according to:

- **LOCATION**: companies in Montreal, Toronto, Halifax, Vancouver, Saskatoon, Winnipeg and Edmonton were selected for consulting in-person; telephone consultations were conducted with companies with which in-person meetings could not be arranged
- **SIZE**: companies ranging in size from large (over 100 employees), mid-sized (30 to 50 employees) to small (less than 30 employees) were contacted
- **POSITIVE PARTICIPATION**: 94 firms were contacted and approximately half responded positively; consultations were arranged with 42 companies and institutions

Participation

The demographics of the companies and organizations that were interested in participating are summarized below:

STAKEHOLDER TYPE		NUMBER OF EMPLOYEES					PROVINCE						
Company	Academic Institution	<20	20-50	50-100	100+	n/a	AB	BC	MB	NS	ON	QC	SK
36	6	8	9	1	8	16	3	9	1	1	9	15	4

The participation rate was 45%, with smaller biotechnology companies more responsive than their larger counterparts.

International Industry Overview

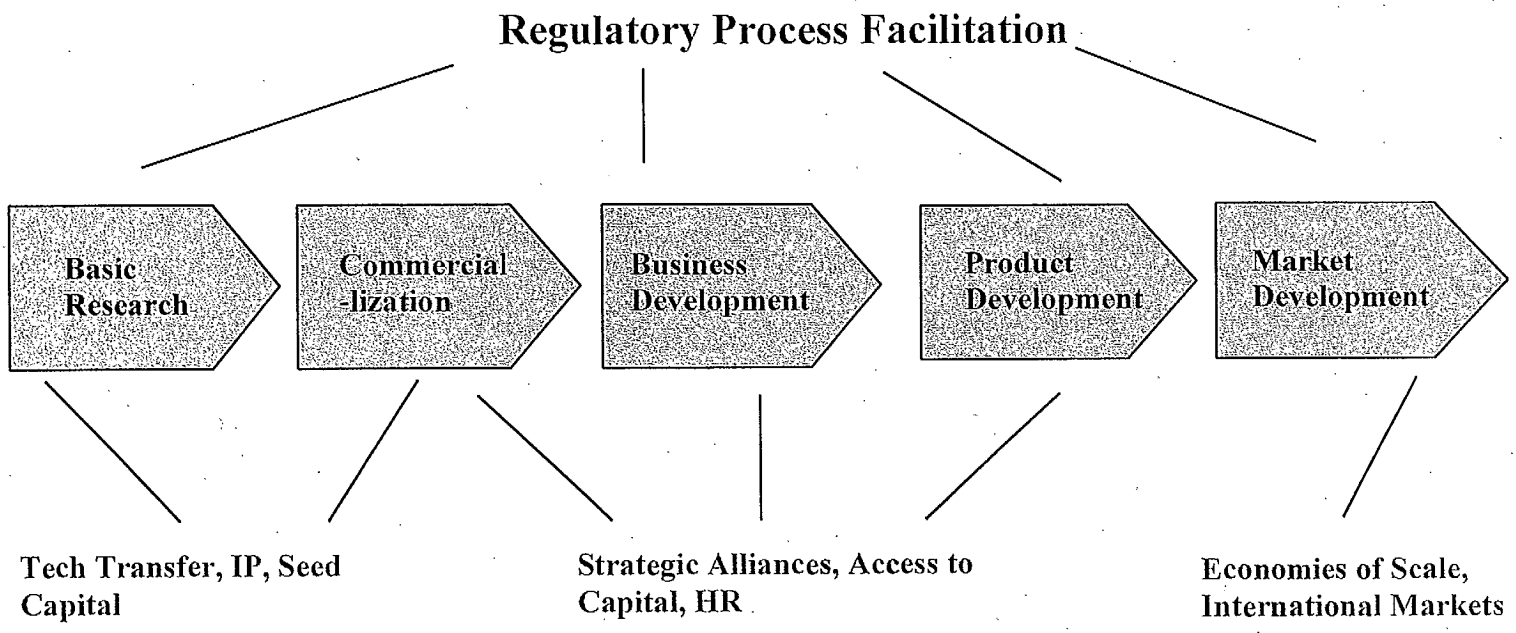
Globally, the biopharmaceutical industry is experiencing an explosive growth as large pharmaceutical firms are seeking alliances with smaller biotech firms. The former are applying their impressive marketing resources to the latter's new technologies. The value of these alliances was over $2 billion in 1998, and expected to continue to increase in coming years. With an imminent technological revolution arising from the impending completion of the Human Genome Project, the players in the industry are positioning themselves to capitalize on this potential cache of new products. This is an important development since the reliance upon single

"blockbuster" products has traditionally been a ubiquitous problem across the industry, making companies highly susceptible to competition, particularly from the manufacturers of comparable substitute products.

Canada's biopharmaceutical industry is second in size only to the United States, however, there is the possibility that the nation could lose its status to rapidly developing European interests, particularly Germany. Cited limitations to growth in Canada include a disadvantageous regulatory structure, inconsistent and unfavourable tax structure, and poor public funding of R&D compared to that benefiting American and European firms.

Value Chain Development

The biopharmaceutical industry's value chain is comprised of five stages: Basic Research, Commercialization, Business Development, Product Development and Marketing Development. The analyses presented herein are based upon companies' focus along the chain, and the effects upon the chain of external factors. Some issues, such as ethical and regulatory issues, affect many or every stage of the chain while others, such as technology transfer, are specific to one stage.



Source: STRATEGIC HEALTH INNOVATIONS, 2000

The changing paradigm of medical care and drug discovery has created the need to capture even more value along each stage of the chain. Since a higher return on investment is generated in

downstream stages of the chain, biopharmaceutical companies are involved in the development of many different types of technologies to widen their grasp on the chain and thus maximize profits. The proliferation of alliances between big pharma and small biotech companies demonstrates the primary method by which companies are extending their capabilities along the entire length of the value chain: by leveraging mutual strengths.

Key Industry and Technology Trends

The genomics revolution of the last few years is often touted as the foundation for much of the new biopharma R&D and product development. The genomics platform having entered a more mature and exhaustive stage, companies are now turning to other technologies to create further value from the sequencing of the human genome. However, genotypic drug discovery is currently facing unique challenges, which include the management of information provided by DNA sequencing data. The science of bioinformatics is evolving to address this gap.
A challenge in the current genomic age is to develop biopharmaceuticals of sufficient specificity and selectivity to interact with identified molecular targets. New technological approaches, such as rational drug design and combinatorial chemistry, are now overcoming some of these difficulties. Monoclonal antibodies, gene therapy, and anti-sense technology also have a role to play in increasing the specificity of drug design.

These new genomic-based technologies promise a more streamlined and effective clinical trials process that will improve time-to-market and bottom line profitability. Furthermore, novel consumer issues will soon arise, such as whether the market and industry are ready for "personalized medicine", and whether society will reject genomic medicine on ethical grounds.

Other areas of medicine and technology are also rapidly converging. Bioinformatic information technology platforms are accelerating the pace of drug target discovery, the Internet is decreasing the time for clinical trial development, and biochips are revolutionizing drug delivery. The next five to ten years in biopharmaceuticals promises to be an exciting time as technological drivers constantly shift and, more importantly, accelerate the drug development process.

Canadian Industry Overview

Canada's rich academic infrastructure provides most of the early stage research that drives new innovation. There are more than 60 academic and medical institutions in Canada that are involved in biomedical research and more than 20 of these are developing innovative specialty areas such as genomics/bioinformatics, diagnostics and therapeutics.

Three types of firms make up the biopharmaceutical industry structure in Canada:

1. Dedicated biotechnology companies developing pharmaceutical products
2. Research-based Pharmaceutical companies

3. "Technology players" or specialized tier of biotechnology firms with technology platforms

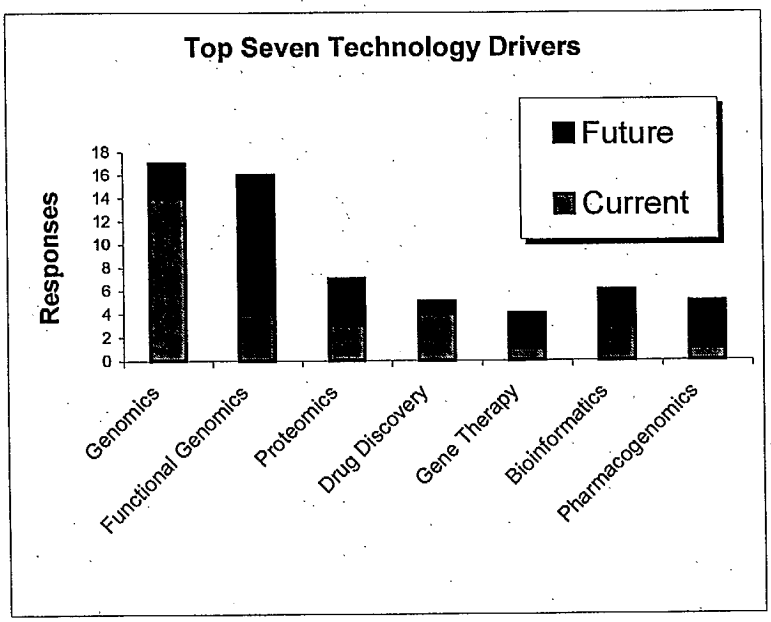
In Canada, there are 85 well established and about 100 early stage, biopharmaceutical firms. Due to the need for distribution networks and scientific expertise, companies tend to be clustered in major cities such as Montreal, Toronto and Vancouver Compared to 1989, when four drugs generated revenues of $15 million, there are now 16 Canadian-developed products approved for sale in Canada. In 1999, sales from 13 drugs reached $207 million.

The Canadian biopharmaceutical industry is experiencing a rapid growth rate of 20% compared to the international growth rate of 10-15%. Future growth and competitive advantage will be sustained by innovation in basic research and by competition based upon product, rather than price.

Consultation Outcomes

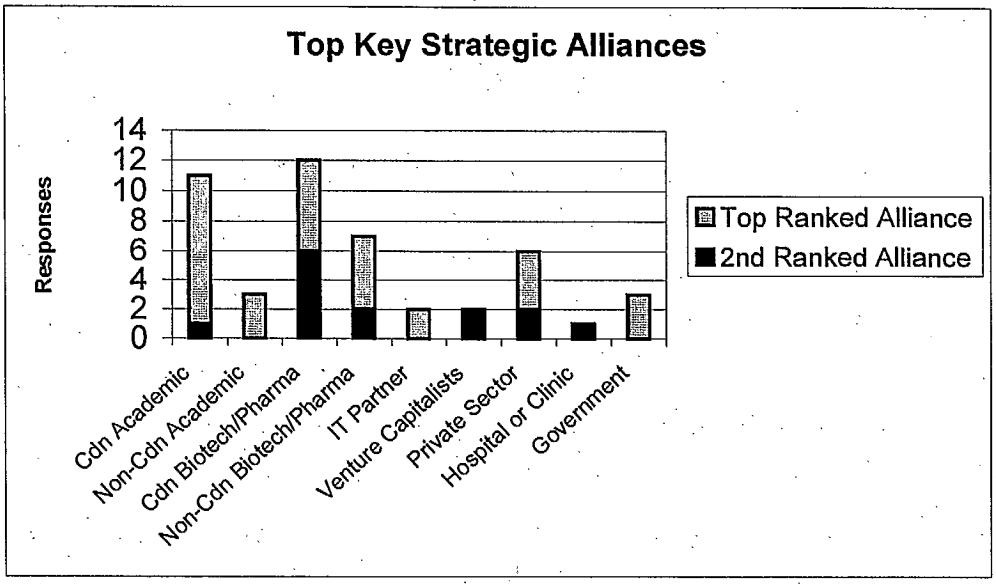
Technology Drivers

When asked to identify the most important Canadian and global technology drivers now, 33% of the industry leaders stated genomics, followed by the general category of drug discovery technologies (10%), functional genomics (10%) and proteomics (7%). Regarding technology drivers for the next five years, the top response was functional genomics (29%), followed by proteomics (10%) and pharmacogenomics (10%).



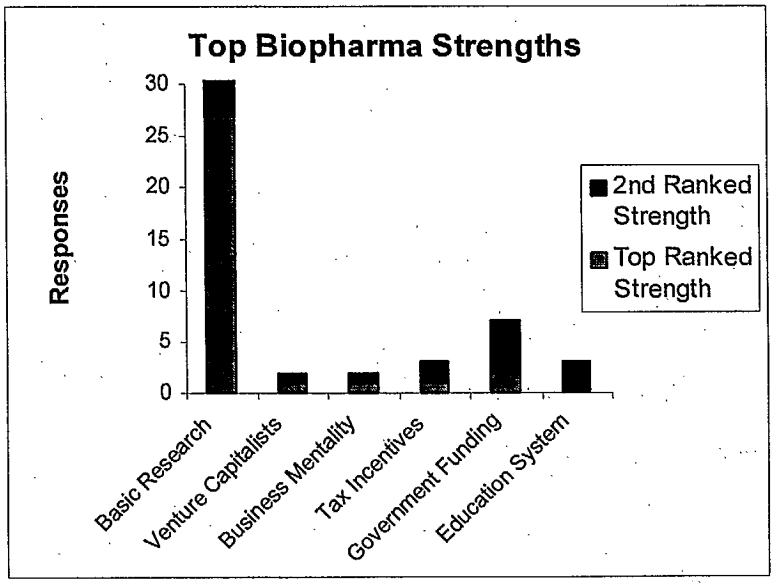
Key Strategic Alliances

During the consultations, CEOs were asked to describe the key relationships and strategic alliances that will contribute to their technological success. Top responses included alliances with Canadian universities and academic institutions (24%) and both Canadian and international biotechnology and/or pharmaceutical companies (26%). Other top ranked alliances include general private sector relationships, government organizations and software companies.



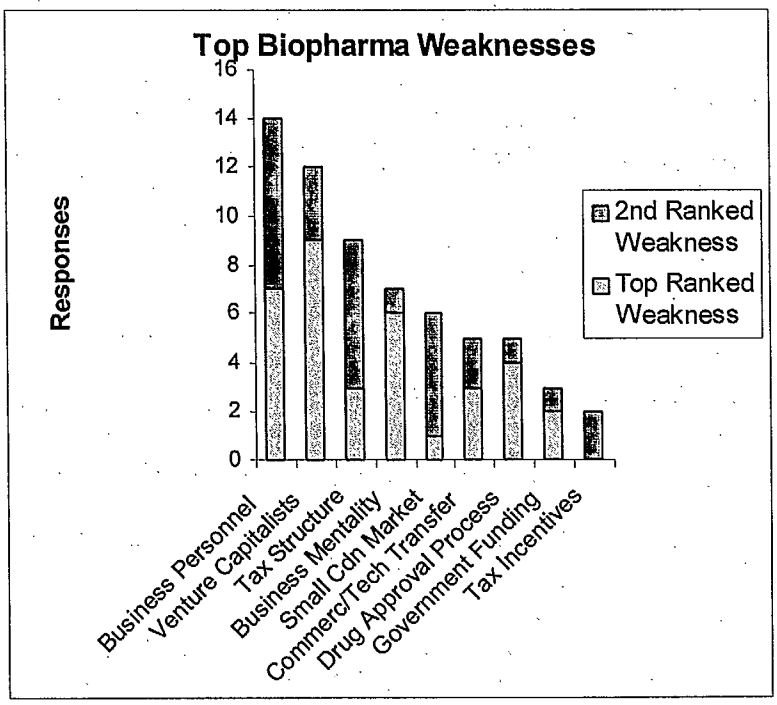
Strengths

The majority of respondents (79%) specified basic research as the number one or two strength in Canada. The availability of government support was cited as an important strength by 17% of those consulted.



Weaknesses

The major perceived weaknesses of the domestic industry include the risk averse behaviour and limited funding of venture capitalists in Canada, especially in the intermediate phases (29%); lack of business skills in the scientific community (33%); and general "business mentality" in Canada (i.e. risk aversion) (17%). Some stakeholders also mentioned better identification of commercializable technologies. Notably, when asked to identify technological weaknesses, there were few responses to this question. Stakeholders overwhelmingly identified technological expertise as an important strength for the industry.



Opportunities

Some of the key opportunities identified for Canada's biopharmaceutical industry are listed below. These are the areas that many participants believed could be capitalized upon to create international competitiveness.

- **POTENTIAL TO BE THE TOP-RANKED COUNTRY WORLDWIDE FOR CLINICAL TRIALS;** Canada has a heterogeneous demographic and a socialized medical structure that is ideal for conducting clinical trials. The formalization of clinical information across wide jurisdictions was viewed by more than half of the participants as an opportunity.

- **INNOVATIVE TECHNOLOGICAL NICHES** are specific market niches that are being overlooked either as a whole or in specific therapeutic areas. For example, drug delivery was cited as an important, stable and growing market and a relatively inexpensive method of innovating new drug products (e.g. $50 million compared to $300 million to develop). Other niches could include a targeted strategy to grow the portfolio for products targeted against a specific disease, e.g. cancer or heart disease.

- **LEAD IN AREAS WHERE CONVERGENCE IS IMPORTANT.** There is an opportunity to formalize cross-sector academic networking and develop leadership in cross-sector research such as bioinformatics.

- **LEAD IN AREAS WHERE KNOWLEDGE AND EXPERTISE ARE IMPORTANT** such as genetic epidemiology in founding populations or disease pathophysiology. There is a general perception that Canada cannot overtake the U.S. in building "better equipment" and that a way to compete was to further develop and capitalize upon the abundant scientific expertise in the nation.

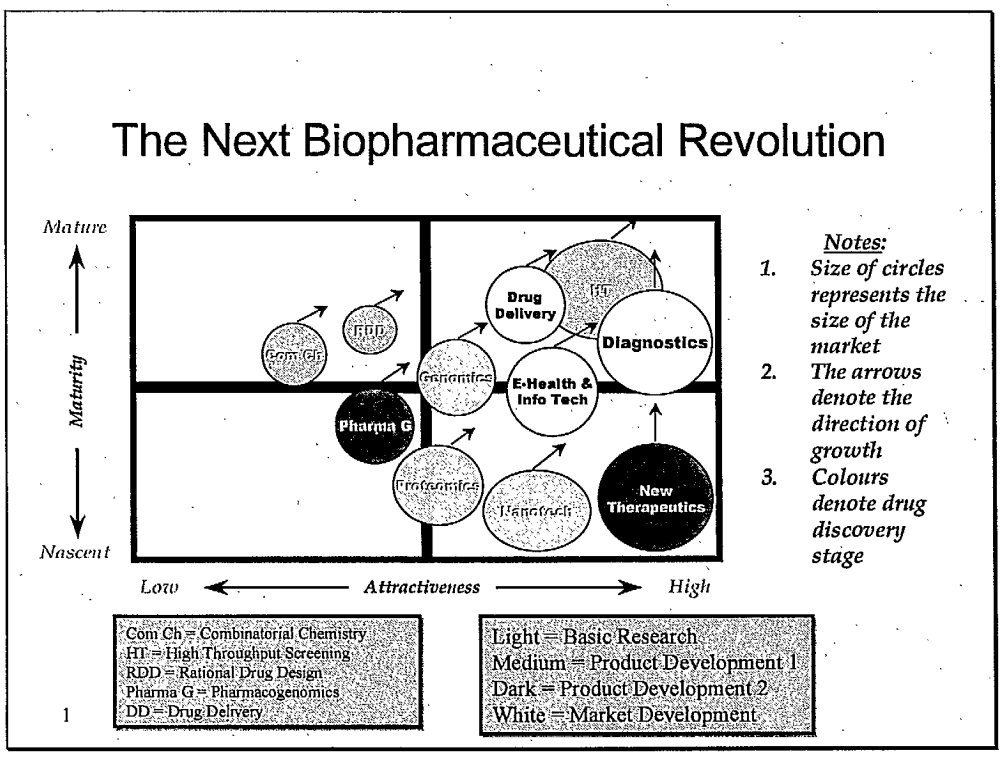
Threats

Some of the threats that Canadian companies face include:

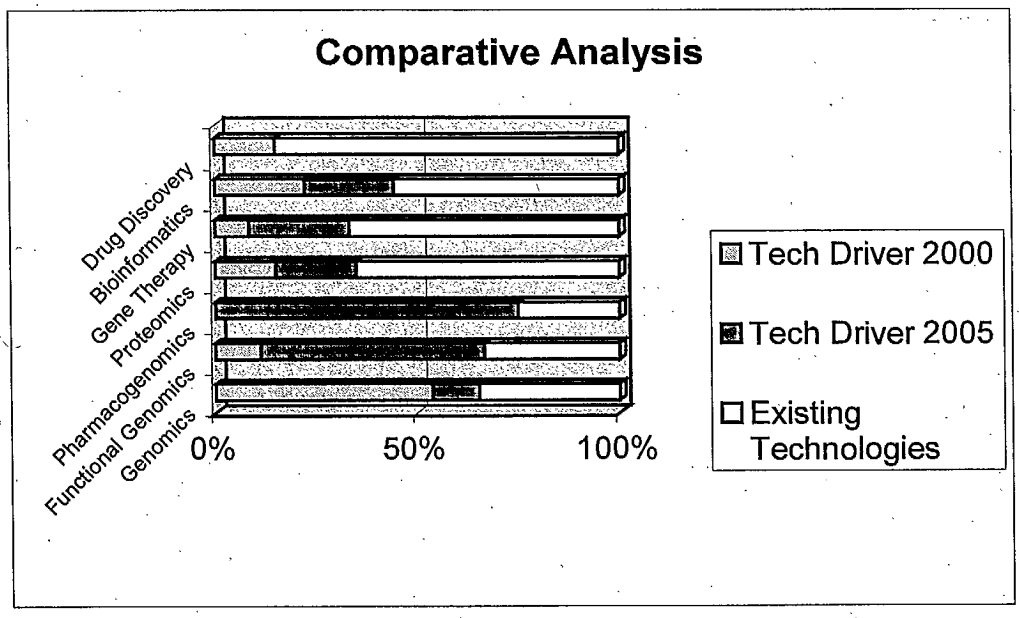
- **INTERNATIONAL THREATS** from countries such as Germany and Ireland that have displaced Canada from 2nd or 3rd spot several years ago.
- **CANADA WILL EXPORT BASIC RESEARCH** and repurchase it at a more developed stage. There was a general concern that Canadian biotechnology will be sold to the U.S. at earlier stages than necessary, and that Canadian companies will therefore not realize the higher returns at later stages of the value chain. There was also a concern that Canada will export its skilled human resources along with the early products.
- **BEING RELEGATED TO "TOOLKIT" COMPANIES** that develop and then sell technologies, rather than develop health care drug products.
- **LOSS OF AN OPPORTUNITY TO DEVELOP A WORLD-CLASS REPUTATION** in a knowledge-based sector that will likely be one of the most important sectors in the global economy.

These threats were viewed as near or immediate-term. Participants indicated their belief that the timeframe for the Canadian industry to remain competitive could be as short as two years.

Comparative Technology Analysis



STRATEGIC HEALTH INNOVATIONS has classified the existing biopharmaceutical technologies according to level of technological maturity and market attractiveness. Some of the emerging technologies that will be highly attractive include nanotechnology, information-technology based platforms and new therapies, such as photodynamic and carbohydrate-based therapies. The mature technologies for which there is high market demand include gene chip technologies involved in high throughput screening and diagnostics and drug delivery systems.



A comparative analysis by STRATEGIC HEALTH INNOVATIONS indicates that there are gaps in the Canadian industry with respect to technologies that are driving the industry forward. For example, pharmacogenomics was identified as the top driver in 2005, while only one out of the 146 firms investigated is actively involved in pharmacogenomics research. Similarly, functional genomics was identified as the second most important technology platform and only 6 out of 146 companies are currently involved in functional genomics.

While stakeholders believe that basic research in technology is Canada's greatest strength, there appears to be a gap between basic research and translation of that research into industrial R&D and product creation.

Summary of Themes

The six most important themes that occurred in many consultations are highlighted below. It is important to note that while there was general consensus on these six themes, there were also some dissenting opinions.

1. **CANADIAN COMPANIES HAVE WORLD CLASS RESEARCH,** however, this value is not being recognized by investors.

2. **NEED FOR IMPROVEMENT IN BUSINESS INFRASTRUCTURE**—such as venture capital, a national industrial funding program and centralized funding for basic research—to capture the value from Canadian innovation

3. **CONVERGENCE OF TECHNOLOGY** is creating the need for cross-sector academic research and increasing the time spent on sourcing strategic partners.

4. **NEED TO IDENTIFY SPECIFIC NICHES IN WHICH CANADIANS CAN COMPETE**, such as clinical trials and innovative technologies, however providing business infrastructure to all companies will make Canadians more competitive.

5. **LACK OF CRITICAL MASS IN TECHNOLOGIES.** One of the most important themes that arose from discussion of the value chain was the lack of critical mass in technological areas in one region or province. While, on the whole, there is critical mass for specialties such as genomics across Canada, the geographical dispersion dilutes the cluster. Due to geographical dispersion and provincial barriers, there is a need for creation of infrastructure and community for industry to interact, learn from each other, collaborate and generate a Canada-wide critical mass.

6. **CANADA RANKS IN THE TOP 5 IN INTERNATIONAL COMPETITIVENESS** but that rank has fallen in the last 5 years.

Recommendations

100% of consulted individuals expressed interest in participating in a Technology Roadmap Initiative. However, several concerns were raised including necessary time commitment, follow-through on results, and the format of the roadmap discussions. Generally, most respondents preferred a small, roundtable format that would feature representation from Industry Canada, e.g. the Deputy Minister and Minister of Industry, the venture capital sector, and government funding agencies, in addition to a broad spectrum of industry participation.

Technology Roadmap

The recommendations that follow arise from specific discussions with participants about the Technology Roadmap Initiative.

1. Implement the Technology Roadmap Initiative for the Canadian Biopharmaceutical Industry. The participation from participants was 100% in favour of the initiative. However, participants did raise concerns about the project as outlined below.

   Action Step: Ensure that participants' concerns are addressed before and during implementation of the Technology Roadmap Initiative.

2. Examine models for different formats for implementing the Technology Roadmap Initiative. Participants indicated that small round-table formats with fewer than 15 people would be most productive.

   Action Step: Examine models such as the Ontario Jobs and Investment Board format of small round-tables in separate pools with final presentations to the entire stakeholder group.

3. Expand the Technology Roadmap to include other industry sectors and technologies that are important for biopharmaceuticals such as information technology, mathematics and physics.

   Action Step: Pursue consultations with biopharmaceutical industry representatives in order to identify the other industries and their representatives that should be included from other industry sectors.

4. Ensure that the Technology Roadmap process is well designed.

   Action Step: Design Roadmap efficiently and effectively to ensure that individuals have a defined role as catalysts and that interactions between biopharma firms and companies from other industries are achieved.

5. Ensure that there is sufficient representation from larger biotechnology companies that can mentor/liaise with smaller ones.

   Action Step: Appoint a stakeholder from a large biotechnology/pharmaceutical company to access representatives from other large organizations.

6. Create an opportunity for follow through.

   Action Step: Ensure involvement of Deputy Minister and Minister so that industry retains confidence in the process.

Business Environment

These recommendations arise from the comments that individuals had regarding the business environment for the Canadian biopharmaceutical industry.

1 Increase the education to consumers, analysts and investors about Canadian biopharmaceutical opportunities in order to recognize the value in the market and implement training programs in the new critical fields of biotechnology.

Action Step: Link together industry, BIOTECanada, the Biotechnology Human Resource Council of Canada and other organizations involved in educating Canadians about biotechnology.

2. Examine alternative models to existing business environment. Some models could include creating technology-specific or therapeutic-specific hubs, concentrating funding on fewer companies with niche and competitive concepts, and creating national tax incentives for industry.

   Action Step: Examine models including Quebec's industrial tax incentives and Ventures West's new $200 M Technology Investment Fund.

1. Implement regulatory planning with foresight to approve future technological products such as pharmacogenomic products.

   Action Step: Liaise with Health Canada's Therapeutic Products Programme to formulate strategies for approving future technological products.

2. Celebrate successes in biopharmaceuticals in order to demonstrate responsiveness and excellence in industry.

   Action Step: Implement programs that identify key Canadian innovators in biopharmaceutical development.

3. Benchmark other countries with regards to business infrastructure for biopharmaceuticals. Some of the potential case studies cited by participants include the U.S. Small Business Granting Program and stock option taxation, Germany/Europe's potential to leapfrog Canada, and Ireland's government focus on decreasing taxes and improving investment opportunities.

   Action Step: Perform international benchmarking studies focusing on the United States and Europe.

4. Create a community or system for linking geographically disparate companies in order to obtain critical mass in technological expertise and knowledge transfer regarding business structure, e.g. availability of provincial and federal government funding programs and incentives.

   Action Step: Develop a national conference aimed at increasing strategic alliances and investment in the biopharmaceutical industry.

5. Ensure accurate and speedy dissemination of information regarding the availability of new funding programs and incentives.

   Action Step: Examine models for information dissemination.

6. Implement training programs in new critical fields of biopharmaceutical technologies.

   Action Step: Link with BIOTECanada and BHRC to develop training programs.

7. Interact with existing programs to highlight the new critical technologies.

   Action Step: Analyze the focus of existing government programs, such as Genome Canada and national and provincial funding programs, such as Technology Partnerships Canada.

Chapter 1: Introduction to the Technology Roadmap

Prior to Industry Canada's launch of a Technology Roadmap (TRM) Initiative in the biopharmaceutical industry, STRATEGIC HEALTH INNOVATIONS was commissioned to perform background research, consultations with a sampling of key stakeholders, an analysis of key findings and make recommendations regarding the approach to the TRM. From across Canada, executives in biophamaceutical companies and academic research leaders were asked about their perspectives on the technological strengths, weaknesses, opportunities and gaps in the industry and their interest in participating in an industry-led, government facilitated TRM. If those consulted expressed concerns or challenges facing the industry, these thoughts were recorded.

1.1 Definition of the Technology Roadmap

A **Technology Roadmap** is a practical business forecasting tool that gives firms in a given sector a way to predict their future technology and product needs, and map out how best to attain them. By involving industry, research, government and other relevant stakeholders, it can help to develop a consensus about a set of needs and the technologies required for meeting those needs. It can also substantially influence the focus of research and development efforts, as well as strategies, policies and programs of stakeholders. By providing better technology planning, a Technology Roadmap can be a key instrument for guiding the growth and international competitiveness of the Canadian biopharmaceutical industry into the 21st century. A Technology Roadmap identifies the new critical technologies required by an industry to meet future market demands and can form the basis from which collaborative technology initiatives are planned and implemented. The ultimate goal is for the Canadian biopharmaceutical industry to gain a competitive advantage in a global market place.

1.2 Background

Industry Canada is currently facilitating industry-led Technology Roadmaps in Medical Imaging, Geomatics, Aerospace and Forestry Products. In the U.K., similar "Technology Foresight" initiatives have been launched in such sectors as health and life sciences, chemicals and pharmaceuticals, information and communication technology, and materials and manufacturing processes. The U.S. has also undertaken Technology Roadmap initiatives in such sectors as integrated manufacturing, microelectronics, new materials and aerospace.

1.3 Purpose of Consultations

The objectives of the stakeholder consultations were:

- To develop an awareness of the Technology Roadmap concept amongst key industry and other stakeholders in the Canadian biopharmaceutical sector
- To define existing technology capabilities and gaps in the Canadian biopharmaceutical sector (industry and research community)
- To identify critical technology needs and core competencies over the next five to ten years which must be developed to meet future market demands, and where Canada should position itself
- To ascertain the interest of stakeholders in actively participating in a Technology Roadmap Initiative proposed for the Summer 2000
- To present recommendations to Industry Canada's Life Sciences Branch

1.4 Methodology

In general, the participation from the biotechnology and pharmaceutical industries was positive. Prospective companies and institutions to be consulted were selected according to:

- **LOCATION**: companies in Montreal, Toronto, Halifax, Vancouver, Saskatoon, Winnipeg and Edmonton were selected for in-person consultation; telephone consultations were conducted with companies with which in-person meetings could not be arranged
- **SIZE**: companies ranging in size from large (over 100 employees), mid-sized (30 to 100 employees) to small (fewer than 30 employees) were contacted
- **POSITIVE PARTICIPATION**: 94 firms were contacted and approximately half responded positively; consultations were arranged with 42 companies and institutions

There are an estimated 85 established biopharmaceutical firms, and over 100 start-up firms in Canada (Life Sciences Research Investments, *Canadian Biopharmaceutical Companies*, 2000). STRATEGIC HEALTH INNOVATIONS consulted 42 industry executives and academic leaders of the biopharmaceutical industry in Canada during March 2000. The following table is a summary of the participating companies. Appendix 1 contains company contact information.

TABLE 1: COMPANIES AND INSTITUTIONS CONSULTED

COMPANY/INSTITUTION	TECHNOLOGY PLATFORM	CONTACT	CITY	PROV
Angiogene Inc.	Radiopharmaceuticals	Francois Bergeron	Montréal	QC
Angiotech Pharmaceuticals Inc.	Angiogenesis Inhibitor/Proteomics	Ken Mellguist	Vancouver	BC
Antalium Inc.	Genomics	Kazimierz Babinski	Montréal	QC
Base4 Inc.	Software for Information Management	Martin Sumner-Smith	Mississauga	ON
BioStar Inc.	Immunopharmaceuticals	Stephen Acres	Saskatoon	Sask
BioTools Inc.	Diagnostics/Genomics	Gordon Stranks	Edmonton	AB
Bregma International	Hardware (Medical/Dental Tools)	Assem Hedayat	Saskatoon	Sask
Biotechnology Research Institute (NRC)	Drug Design	Michel Desrochers	Montréal	QC
Cangene Corp.	Ab-based Immunotherapy	Kim Wong	Winnipeg	MB
CV Technologies Inc.	Therapeutics ("ChemBioPrint" technology)	Jackie Shan	Edmonton	AB
Chemical Computing Group	Software for Drug Development	Bill Hayden	Montreal	QC
ConjuChem Inc.	Drug Delivery (/Bioconjugation)	Daffy DuFresne	Montreal	QC
Exogen Neurosciences Inc.	Drug Discovery/Therapeutics	Michael Atkin	Montréal	QC
Hoffmann-La Roche Ltd.	Drug Discovery / Diagnostics	Roger Halashyn	Mississauga	ON
Hospital for Sick Children	Therapeutics	Lap Chee Tsui	Toronto	ON
Hybrisens Ltd.	Recomb. DNA/Proteomics/Therapeutics	Ezekiel Shami	Toronto	ON
IGT Pharma Inc.	Comb.chem./High throughput scr/drug disc.	Bruce Schmidt	Vancouver	BC
Immucon Inc.	Therapeutics (contraceptives)/Diagnostics	Alain Bossé	Montréal	QC
Innovation Place	Various depending on Company	Doug Tastad	Saskatoon	Sask
International Wex Technologies Inc.	Therapeutics / Diagnostics	John Othoff / Donna Shum	Vancouver	BC
Key Molecular Corp.	Drug discovery / Software	Joseph Tedesco	Toronto	ON
Lorus Therapeutics Inc.	Functional Genomics/Immunotherapeutics	Philippe Lacaille	Toronto	ON
Methylgene Inc.	Functional Genomics/High throughput scr.	Don Corcoran	Montréal	QC
Mycota Biosciences Inc.	Therapeutics	Marc Lussier	Montréal	QC
NPS Allelix Corp.	Proteomics		Toronto	ON
Neurotrophic Bioscience Inc.	Therapeutics	Anthony J. Giovinazzo	Etobicoke	ON
Nortran Pharmaceuticals Inc.	Drug Discovery	Michael Walker	Vancouver	BC
Paladin Labs Inc.	Therapeutics	Jonathan Goodman	Montréal	QC
PharmaDerm Laboratories Ltd.	Therapeutics / Drug Delivery	Marianna Foldvari	Saskatoon	Sask
Phenogene Therapeutics Inc.	Functional Genomics / Transgenics	Robert Knapen	Montreal	QC
Quantanova Inc.	Photodynamic Therapy	Michael Winther	Kentville	NS
R&D Canada's Pharma	Drug Discovery	Zenek Dybka	Hamilton	ON
Replicor Inc.	Recomb. DNA / Gene Therapy	Jean-Marc Juteau	Montréal	QC
Samuel Lunenfield Research Institute	Genomics / Proteomics / Bioinformatics	Alan Bernstein	Toronto	ON
Spectral Diagnostics Inc.	Diagnostics (Cardiac)	Douglas Ball	Toronto	ON
StemCell Technologies Inc.	(Provides reagents/products for research)	Eric Atkinson	Vancouver	BC
Supratek Pharma Inc.	Drug Delivery	Valeri Alakov	Montréal	QC
Tai-can Technologies	Bioinformatics	Greg Kamanka	Vancouver	BC
TerraGen Diversity Inc.	Drug Discovery / Recomb. DNA	Julian Davies	Vancouver	BC
Theratechnologies Inc.	Therapeutics	André de Villers	Montreal	QC
University of Alberta	Drug Discovery / Therapeutics	Mohsen Daneshtalab	Edmonton	AB
Vancouver Hospital & Health Sciences Centre	Therapeutics / Gene Therapy	Bernie Bressler	Vancouver	BC

1.5 Company Demographics

Participation

The demographics of the companies and organizations that participated in the consultations are summarized below:

FIGURE 1: STAKEHOLDER DEMOGRAPHICS

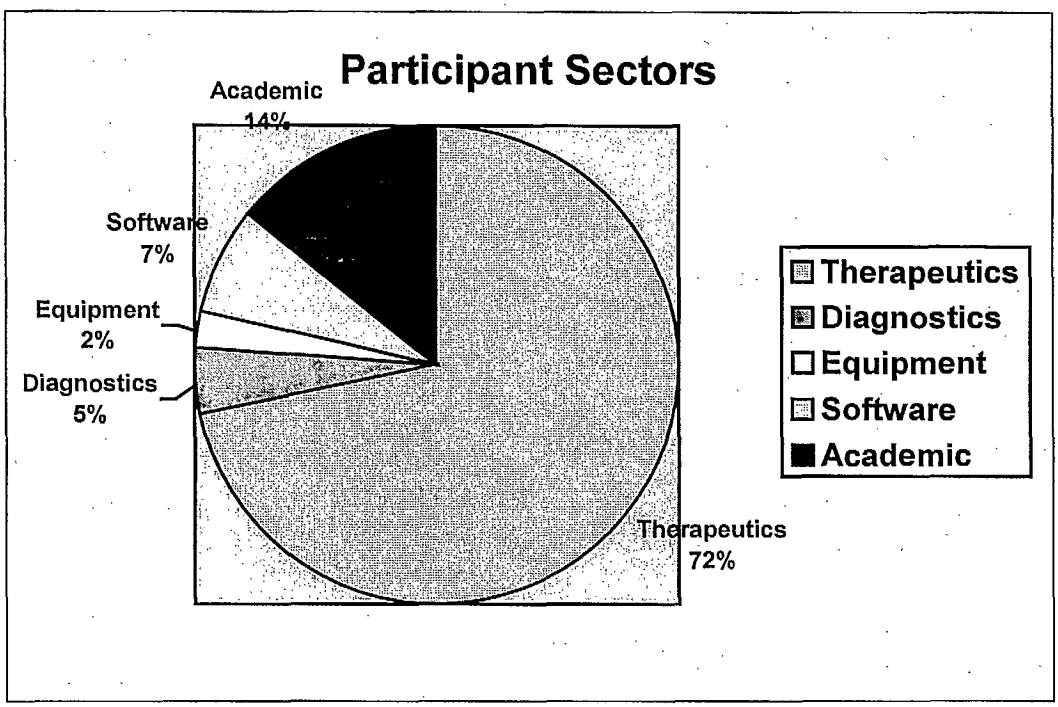
STAKEHOLDER TYPE			NUMBER OF EMPLOYEES				PROVINCE							
COMPANY	ASSOCIATION	ORGANIZATION	20	20-50	50-100	100+	AB	BC	MB	NS	ON	QC	SK	
36	6	8	9	1	8	16	3	9	1	1	9	15	4	

The participation rate was approximately 45%, with smaller biotechnology companies more interested in participating in the consultation process. The participation rate was representative of biopharmaceutical company clusters in individual provinces.

Industry Subsectors

The organizations consulted fell into four categories: diagnostic product companies, software/information technology companies, therapeutic product companies, academic institutions and equipment and supplies companies.

FIGURE 2: PARTICIPANTS BY INDUSTRY SUBSECTOR



Chapter 2: International Industry Overview

Chapter 2 reviews the international biopharmaceutical industry. There are two parts in Chapter 2: Part A is an overview of industrial trends and Part B analyzes the key technologies that are being developed by industry. Chapter 3 expands the analysis to the Canadian context, utilizing background research, as well as consultation outcome information, to identify the key technological strengths and gaps in biopharmaceutical product development.

Part A: Overview

2.1 Explosive Growth

Successful biopharmaceutical firms have typically evolved from small research-intensive organizations. The industry can boast stunning success stories, ranging from BiochemPharma in Canada to Amgen in the U.S. These former research groups have grown into fully integrated pharmaceutical firms in their own right, an uncommon occurrence in the biotechnology industry. Their product portfolios, derived from broad capabilities in diverse technology platforms, consist of novel, premium priced drugs. Though such drugs constitute a small product base, they can render significant revenues. For example, Amgen's 1998 revenue of almost $US 3 billion was derived almost entirely from two main biopharmaceuticals: epoetin alfa (recombinant human erythropoietin) for anemia management, and filgrastim for chemotherapy induced neutropenia. Success in this industry has thus traditionally followed a research-to-product pathway, but suffers from limited product diversity.

TABLE 2: TOP BIOPHARMACEUTICALS IN 1997

Product	Developer	Marketer	Indication
Procrit	Amgen	Johnson & Johnson	Anemia
Epogen	Amgen	Amgen	Anemia
Neupogen	Amgen	Amgen	Neutropenia
Epivir	Biochem Pharma	Glaxo-Wellcome	HIV
Humulin	Genentech	Eli Lilly	Diabetes
Intro	Biogen	Schering-Plough	Cancer
Engenx- B	Genentech	Smith Kline Beecham	Hep B Vaccine
Betaseron	Chiron/Berlex	Berlex/Schering AG	Multiple Sclerosis
Genotropin	Genentech	Pharmacia & Upjohn	Growth
Ceredase	Genzyme	Genzyme	Gaucher's

Source: Ernst & Young, Bridging the Gap 99

From an uncertain fledgling sector just twenty years ago, the biopharmaceutical industry has experienced explosive recent growth, markedly so over the last decade, with a seven-fold increase in worldwide sales.

Biopharmaceuticals account for 5% of the total world drug market, a share that is expected to triple to 15% by 2005. Fifty-four biopharmaceutical products have been approved for sale in the United States; and, in 1998, about a quarter of the 39 drugs approved by the FDA were of the biopharmaceutical category. About 30-50% of the drugs currently in the international product pipeline can be characterized as biopharmaceutical (Boston Consulting Group, 1999).

Canada

Presently in Canada, there are 85 well established and about 100 early stage, biopharmaceutical firms. Compared to 1989, when four biotech drugs generated revenues of $15 million, there are now 16 products approved for sale in Canada in 2000. Sales from just 12 of those drugs have reached $207 million. Canadian biopharmaceutical companies are demonstrating their rapid rate of innovation with 372 products under development. The top four major therapeutic R&D categories are cancer, infectious disease, central nervous system and cardiovascular illness. There is much room for further expansion; Canadian companies are actively seeking opportunities to develop specialties in therapeutic markets that have unmet needs, e.g. cancer and AIDS (Life Sciences Research Investments, *Canadian Biopharmaceutical Companies*, 2000).

Despite these promising indications that the Canadian biopharmaceutical industry is maturing rapidly, the pharmaceutical companies are still the dominant players in the sector with significantly higher market capitalization and greater product revenues than their biopharmaceutical counterparts. Therefore the trends affecting pharmaceutical companies are the drivers behind the evolution of the total biopharmaceutical sector.

TABLE 3: PHARMACEUTICAL AND BIOPHARMACEUTICAL REVENUES

Top Pharmaceutical Firms	Revenue ($ M US)	Top Biopharmaceutical Firm	Revenue ($ M US)
Glaxo-Wellcome	11,600	Amgen	2,303
Merck	11,400	Chiron	1,313
Novartis	11,000	Genentech	967
Bristol-Myers Squibb	9,300	Genzyme	536
Johnson & Johnson	8,700	Alza	466
American Home Products	8,400	Biogen	277
Pfizer	8,400	Immunex	153
Roche	8,000		
SmithKline Beecham	7,400		
Hoechst Marion Roussel	7,400		

Source: The Economist Pharmaceutical Industry Survey, 1998

2.2 Challenges for the Pharmaceutical Industry

The growth in the biopharmaceutical industry stems from the multiple challenges that are forcing the industry to generate growth by aggressively courting new drug development and delivery options, instead of simply relying on new uses for existing products. The impacts of these challenges are discussed below.

Managed Care, the American Market and Cost Containment

Due to the size and profile of the market, the United States health care system contributes to a large proportion of big pharma's profits. The excellent funding base provided by the American National Institutes of Health (NIH) will continue to herald good tidings for global health care developments, as the NIH provides much of the pure research monies indirectly responsible for most new drug formulations. However, the American market is chronically hampered by an inability to contain escalating costs.

An aging North American population that is living longer and suffering from more chronic diseases is driving health care costs up, and changing the profile of market needs. Health insurance, embodying the transfer of purchasing power from the young and well to the sick and elderly, increases the total demand for health services and increases overall health spending. A crisis is pending due to the low general population growth accompanying an aging population. Demographic projections suggest an increasing inability of the public revenue base to support the higher demand of tomorrow's populous elderly. Because of their unique cost-effectiveness, biopharmaceuticals hold promise as being especially valuable in curtailing future overall health spending on a society level.

The rise of managed care, in an attempt to provide a seamless continuum of health care service delivery from primary through to tertiary care, will be a key driver behind biopharmaceutical developments well into the later years of this decade. Enrolment in managed health care is surging; now almost 80% of employed Americans are covered by an HMO, a preferred provider organization, or a point of service plan. Managed care cost containment strategies, such as formularies, drug utilization reviews and generic substitutions, require pharmaceutical manufacturers to become more involved in downstream activities. The advent of managed care will likely affect the industry through its requirement for greater company involvement at more points along the research-to-market pathway, including a greater role in the education of all the key health care stakeholders: patients, payers, and providers.

Patent Expiration

As discussed, generic substitution is a cost-saving managed care strategy. Within the next decade, generic products will capture significantly more market share and may represent up to 85% of all written prescriptions. As well, the time period is shrinking rapidly during which the first drug in a given therapeutic class remains the sole drug in that class. This represents a

significantly shortened product life cycle, leaving a very short time period for a drug developer to recoup its R&D investments. Table 4 summarizes the products that are most threatened by this development.

TABLE 4: TOP PRODUCTS THREATENED BY PATENT EXPIRATION

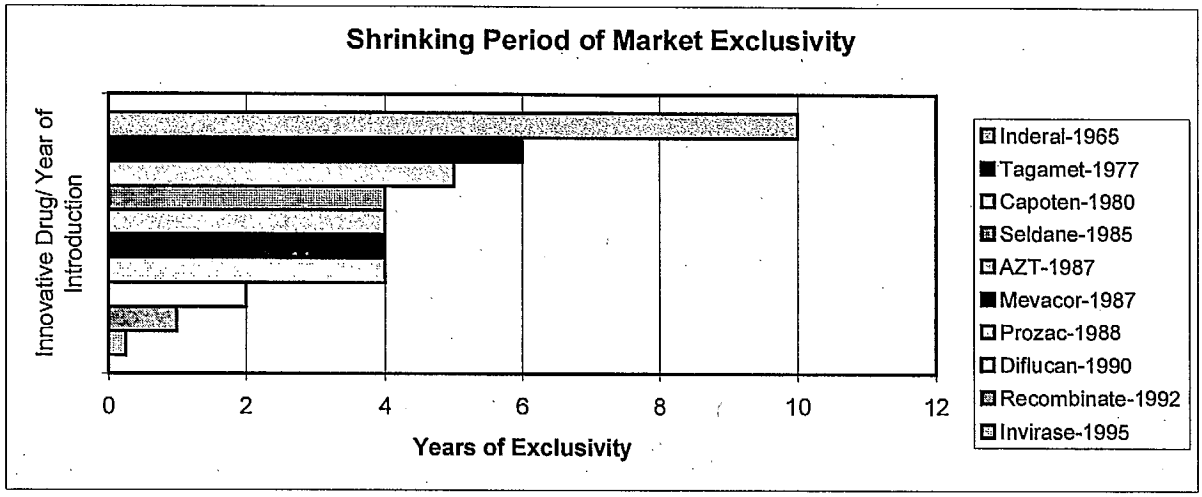
Year of Expiration	Patent Product	Yearly Sales ($M US)	Patent Holder
2000	Neurontin	574	Warner-Lambert
	Procardia XL	492	Pfizer
	Hytrin	486	Abbott
	Ceftin	404	Glaxo Wellcome
2001	Prilosec	3350	Astra Zeneca
	Pepcie	585	Merck
	Allegra	425	Aventis
	Accutane	424	Roche
2002	Claritin	1290	Schering-Plough
	Relafen	379	SmithKline Beecham
	Accupril	353	Warner Lambert
	Axid	265	Eli Lilly

Source: Chemical and Engineering News, 2000

Shorter Periods of Exclusivity

Because of the shrinking product life cycle, it is becoming more difficult to maintain leadership in a therapeutic class through proprietorship of a product. For example, Tagamet—an anti-ulcer agent—had a six year lead on its arch competitor, Zantac. In comparison, Recombinate, a biopharmaceutical clotting factor for hemophilia introduced in 1992, had less than one year as the first mover before the launch of Kogenate. Invirase, the first of a new class of anti-viral pharmaceuticals known as protease inhibitors, had only three months before Norvir, also a protease inhibitor, came onto the market. A necessary strategy will be the establishment of wider product portfolios.

FIGURE 3: MARKET COMPETITION DECREASES EXCLUSIVE TIME ON MARKET



Source: Pharmaceutical Industry Profile, 1999, PhRMA

Fewer Blockbuster Drugs in Pipelines or on the Horizon

The need for diversity in the product portfolio is confounded by a dearth of imminent big-impact drugs. The rise of generic drug manufacturers and the launch of "me-too" products that add incremental value to drug portfolios, rather than the development of innovative blockbuster drugs, are proving to be challenges for big pharma. This challenge is leading to a wave of consolidation across the industry in an effort to gain efficiencies in R&D and to widen product pipelines, a trend that is elucidated in Table 5. The result is the emergence of giant pharmaceutical companies with much larger market shares.

TABLE 5: RECENT MERGERS AND ACQUISITIONS

Recent Mergers and Acquisitions
2000
Glaxo and SmithKline
Monsanto and Pharmacia & Upjohn
Pfizer and Warner-Lambert
Affymetrix and Genetic Microsystems
1999
Millennium Pharmaceuticals and LeukoSite
Roche and Genentech
Warner-Lambert and Agouron
Johnson & Johnson and Centocor
1998
Hoechst AG and Rhone-Poulenc Rorer
Sanofi SI and Synthelabo
Zeneca and Astra

Source: STRATEGIC HEALTH INNOVATIONS, 2000

Maintaining critical mass and sustaining future growth now requires pharmaceutical companies to launch three to five new drugs per year, a milestone that far surpasses historical achievements. As well, in order for a new drug to be considered successful it must generate annual sales of at least $US 200 million. A drug is not considered a blockbuster until it achieves annual sales of $US 1 billion. As a result, big pharma companies are channelling record cash flows from mature product portfolios into R&D, and in-licensing technology from smaller biopharmaceutical firms to remain competitive.

Changing Consumer Landscape

These changes in the business environment are closely tied to wider social changes related to greater public access to information, and, subsequently, more proactive consumer behaviour. Consumer empowerment has been at the core of trends such as decentralized medicine and an increased focus on consumer needs, such as more convenient drug delivery systems. The Internet is transforming the face of health care as it serves to link consumer groups with sources of expert medical information and with products that were previously less available.

Increased consumer empowerment is leading to the emergence of a new breed of drugs targeted at lifestyle issues rather than disease. The last few years have seen the introduction of drugs

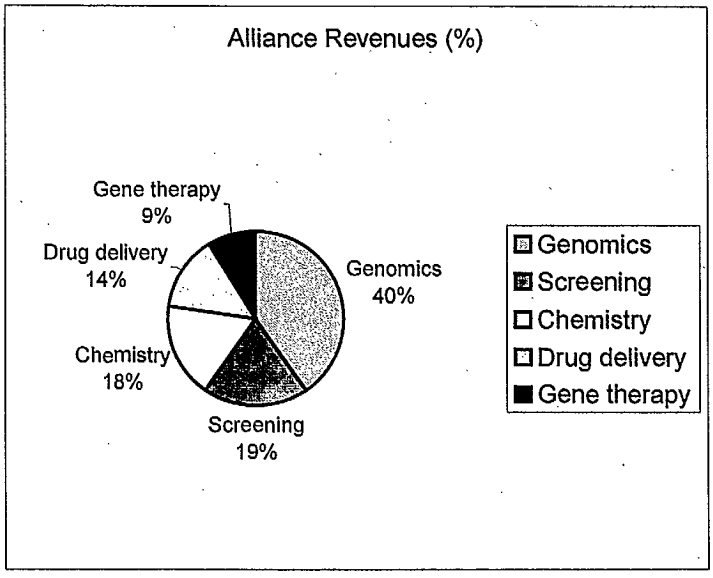
related to sexual enhancement, hair-loss, anti-aging and other "cosmetic" pharmaceuticals. This new market is in addition to that for painful but non-life threatening conditions such as obesity and arthritis. The growing population of elderly is an attractive market for many such lifestyle drugs. The opportunities for premium priced products driven by direct consumer demand is now significantly diverting resources into non-traditional research and development arenas, further altering the goals and approaches of biopharmaceutical companies.

New Technology Platforms

Related to the changes in population profile, social behaviour and medical needs is the accelerating rate of new technology advancements, a direct result of the last decade's thrust to integrate biosciences with commercialism. New technology platforms are changing drug development protocols and are integrating biotechnology into the pharmaceutical sector.

The technology drivers of the biopharmaceutical industry can be identified by observing the types and amounts of investment into biotechnology companies. In 1997, international alliance revenues indicate that the most sought-after technology is genomics (41%), followed by screening (19%), chemistry (18%), drug delivery (14%) and gene therapy (8%). This breakdown is summarized in Figure 4.

FIGURE 4: ALLIANCE REVENUES BY TECHNOLOGY



Source: Recombinant Capital, Signals

Functional genomics permits the disease target to be better identified, allowing more drugs to be targeted at narrower patient populations. It is anticipated that this development will result in

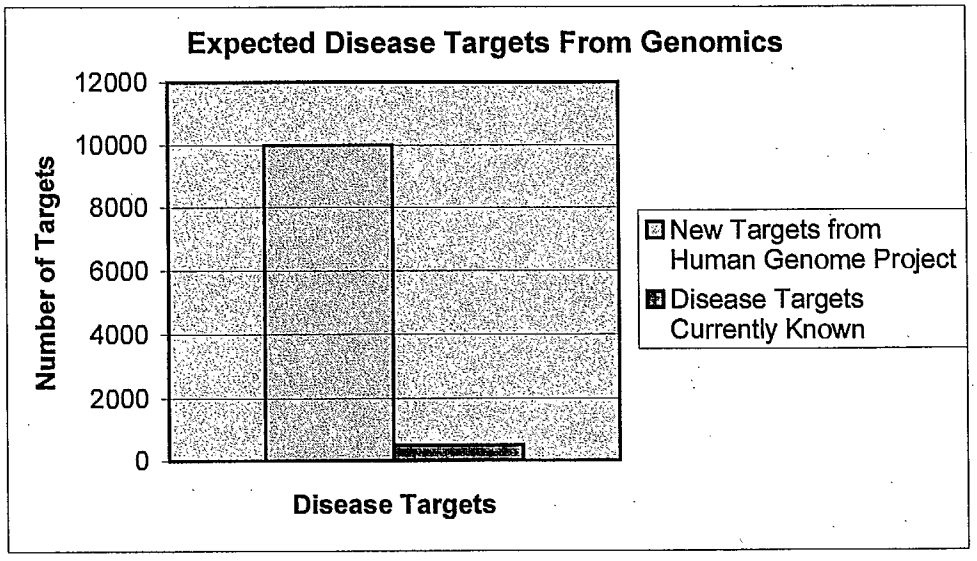
reduced economic barriers because of increasingly more efficient R&D, and a subsequent increase in the availability of innovative therapies.

The biomedical industry is poised for explosive growth—and a revolution—with the imminent completion of the mapping of the human genome. According to the Boston Consulting Group, the sequencing of the human genome is expected to add an additional 3,000 to 10,000 new drugs, compared to the 500 targets the pharmaceutical industry has focused on over the last 50 years, and the 1,000 drug types currently in the global pharmaceutical pipeline.

Evidence of the revolution comes from the dramatic increase in alliances between biotechnology start-ups and pharmaceutical companies. From 1994 to 1997, the value of alliances between biotechnology and U.S. pharmaceutical companies more than tripled, from $1.4 billion to $4.5 billion as pharmaceutical companies attempted to align themselves with young innovative companies. This trend is even more evident in the genomics sub-sector as the number and value of pharmacogenomic alliances has also increased dramatically, and is expected to more than double from $1 billion in 1998-1999 to $2.5 billion by the year 2002 (Biovista *Industry Review and Company Database*, 1999).

It is evident that policy makers of the biopharmaceutical industry foresee their fortunes to be tied to the imminent advances in biotechnology. Further synergy between these types of companies can be expected in coming years as a flood of new genetic data begins to enrich pure and commercial research endeavours.

FIGURE 5: INCREASING NUMBER OF NEW DRUG TARGETS FROM GENOMICS



Source: Pharmaceutical Industry Profile, 1999, PhRMA

Clearly, innovative approaches are required to manage this wealth of data: DNA biochips, rational drug design, bioinformatics and molecular mining are already being incorporated into marketable products to facilitate drug discovery and development.

Summary

Pharmaceutical companies have traditionally maintained their success through the identification and patent protection of lead compounds. However, biotechnology companies have now established themselves as the innovators of new technology platforms, such as combinatorial chemistry, high-throughput screening and bioinformatics, thus enabling the patenting of many variations of a compound. The commercial application of these patents has resulted in a wave of alliances between pharmaceutical and biotechnology firms, creating a biopharmaceutical industry subsector.

The focus of the pharmaceutical industry has changed from specific model systems to speed of discovery of molecules and their biological pathways. Correspondingly, collaborations on technology platforms that increase throughput are essential and indeed unavoidable. The goal of pharma interests is to use biological technologies to enter the market as first-to-patent interests, and to subsequently block competitors.

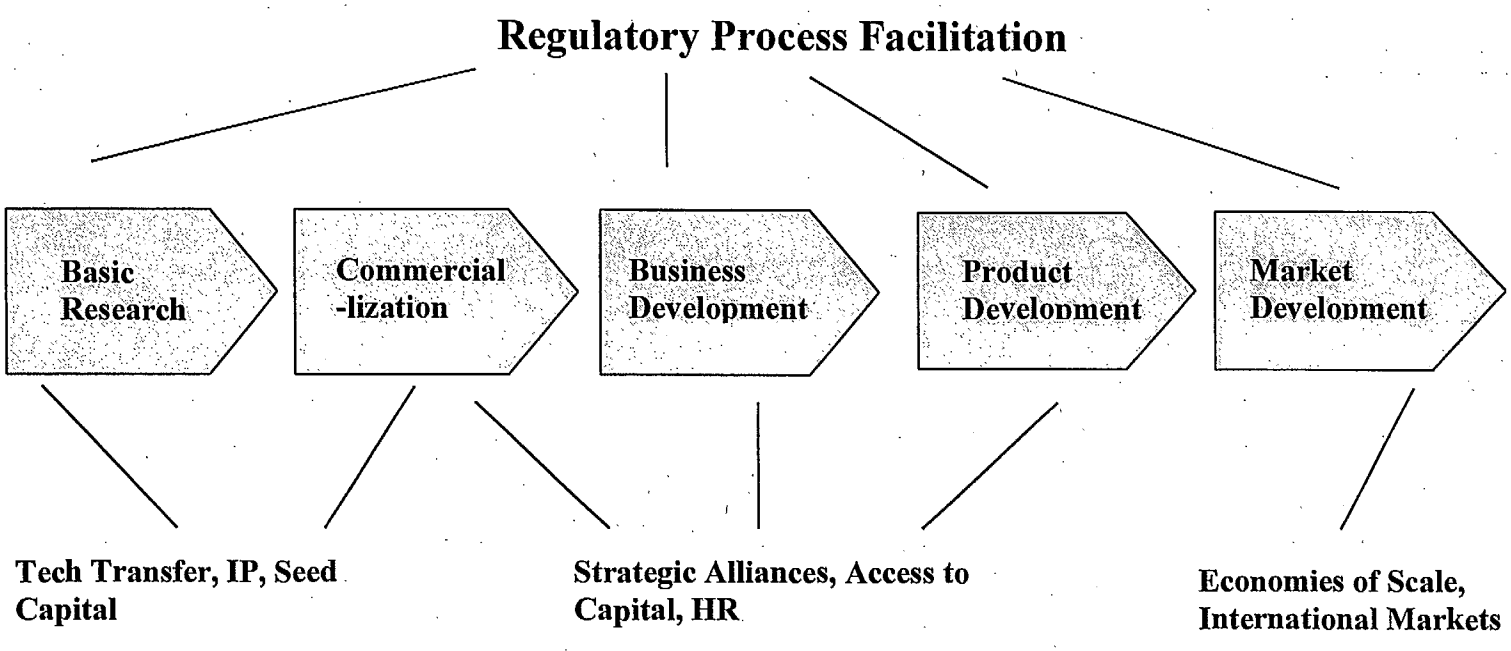
Over the next 5 to 10 years, the success of pharmaceutical companies will depend largely upon their ability to source biopharmaceutical R&D. The R&D strategy of large, multinational pharmaceutical enterprises (MNEs) is reflected in the already significant (and rising) spending on biopharmaceutical R&D.

2.3 Industry Value Chain

From seed research to a marketable biopharmaceutical product, there are key milestones that create value. The achievement of these milestones set the tone for progressive development. A value chain analysis helps to identify the drivers behind market opportunities and technological trends. By classifying technologies according to a value chain designed by STRATEGIC HEALTH INNOVATIONS (see Key Technological Drivers and Trends), it is possible to identify where technologies provide the most value. In some ways analogous to the drug discovery process, value chain analysis captures consumer and market needs and demands, such as direct-to-consumer marketing as part of market development, that an analysis of the technologies of the drug discovery process alone could not provide.

The biopharmaceutical industry's value chain is composed of five stages: Basic Research, Commercialization, Business Development, Product Development and Marketing Development. Some issues, such as ethical and regulatory concerns, affect many or every stage of the chain, while others, such as technology transfer, are specific to one stage. The following is a summary of trends affecting the stages of the biopharmaceutical value chain.

FIGURE 6: BIOPHARMACEUTICAL INDUSTRY VALUE CHAIN



Source: STRATEGIC HEALTH INNOVATIONS, 2000

Stage 1: Basic Research and Innovative Technology

The value created by biopharmaceuticals is unquestioned. Moreover, Canada's aging population will only support the need for further development and advancement of the industry over the next decade. Innovative research in biotechnology, conducted at universities, hospitals, and research institutes, is the spark to the biopharmaceutical industry. The international biotechnology market will exceed $50 billion by 2005, with 75% of the market dominated by health care. In Europe and North America, about 800 biopharmaceutical firms now employ 60,000 workers. The majority (two-thirds) of such firms are located in the United States, a market that accounts for almost half of the worldwide biopharmaceutical sales ($US 15 billion in 1998).

According to Ernst & Young, the United States is the market leader, followed by Europe and Canada (Ernst & Young, 1999). The recognized dominant position of American biotechnology companies is in large part due to extensive federal funding of basic research through the National Institutes of Health (NIH) that created high quality labs and human resources. In 2001, the

amount of American funding for early-stage biomedical research will be $US18.8 billion. In comparison, in 2000 there is $500 million in federal funding available through the Canadian Institutes of Health Research (CIHR) program.

Stage 2: Commercialization and Technology Transfer

The biopharmaceutical sector is unique as it is entirely dependent upon an efficient lab-to-market pathway. Technology transfer has therefore become a pervasive term in government, media, academia and commerce. The United States has outperformed other countries in technology transfer due to factors such as a well-cultivated entrepreneurial culture within academic institutions, critical mass of biotechnology companies and ease of raising money in the capital markets. However, the length of time required for the commercialization period and high R&D costs are still contributing to overall losses for global biopharmaceutical companies. In the United States, 16 of the 169 public companies are profitable, compared to 2 out of 22 public firms in Canada.

Innovative academic R&D efforts are geared towards obtaining patent protection and finding the proper commercial vehicle, such as licensing and marketing. Canada's commercialization efforts are paying off in successes, especially in the field of medical research that is leading the nation in commercialization outcomes. The industrial sector is also increasingly funding R&D in academic universities, providing a total of 12% of funding in 1997 compared to 8% in 1990 (Expert Panel on the Commercialization of University Research, *Public Investments in University Research: Reaping the Benefits*, 1999).

Biomedical spin-off companies are increasingly driving Canada's economic engine but more resources need to be dedicated to commercialization efforts in academic institutions.

Significant IP issues, such as the ethical aspects of patenting human DNA sequences, also loom on the horizon. The importance of a global regulatory framework is therefore evident.

Stage 3: Business Development, Access to Capital and Strategic Alliances

The largest source of later stage funding for biopharmaceutical firms comes from pre-commercial strategic alliances. According to STRATEGIC HEALTH INNOVATIONS, only 10% of a company's capital in the first ten years is funded by venture capital, while approximately 40% of the remaining capital is funded by public equity, and 50% provided by big pharma.

TABLE 6: RISK ADJUSTED COST OF CAPITAL

Stage of Venture (RSI)	Expected Return (%)
Seed	80
Start-up	60
First-stage	50
Second-stage	40
Third-stage (mezzanine)	30
Bridge	25

Source: STRATEGIC HEALTH INNOVATIONS, 2000

Generally, there has been considerable growth in venture capital and public equity available to the biotechnology sector in Canada. However, this growth has slowed since 1997 as many North American investors have migrated to the information technology sector where gestation periods are much shorter.

Although pharmaceutical companies are under pressure to seek out biopharmaceutical alliances (due to declining R&D effectiveness and increasing competition), biotechnology companies can have their bargaining power reduced because of lack of access to early stage capital and equity markets for later stage capital. The farther along the development phase that biopharmaceutical companies can reach, the higher the royalty revenues they can realize from their products. If biopharmaceutical companies can reach Phase III of clinical development or negotiate co-marketing rights, they can realize up to 50% of the royalty revenues.

TABLE 7: ROI FOR PRODUCT DEVELOPMENT STAGES

Product Development Stage	Return on Investment (%)
Basic Research	25
Phase I Clinical Trials	5 – 10
Phase II Clinical Trials	10-15
Phase III Clinical Trials	15 – 25
Manufacturing and Marketing	35 +

Source: NBAC, *Sixth Report,* 1998.

Stage 4: Product Development, Clinical Trials and Regulatory Process

The process of drug development, clinical research, approval and delivery can take as long as 12 to 15 years. Regulatory delays can significantly increase the costs of bringing a product to market. Each day lost to delays represents $1 to $6 million lost in sales. Product approval in the United States now averages 366 days compared to the European Medicines and Evaluation Agency (EMEA) average of 370 days. In the United States, legislative measures, such as the Orphan Drug Act, have also provided incentives for the development of drug targets to treat rare diseases. Other product development trends include the increasing tendency for companies to contract out research services and outsource clinical development. The ensuing result is an increased reliance on contract research organizations (NBAC, *Sixth Report*, 1998).

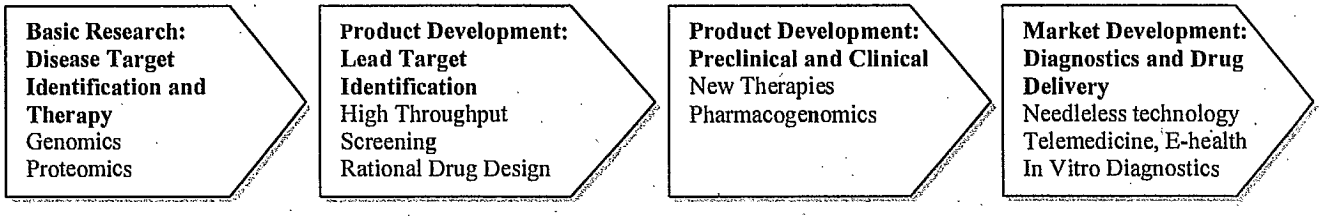
Stage 5: Market Development, Manufacturing and Marketing Capabilities

Due to the significant expenditures involved in marketing a product, most biopharmaceutical firms do not plan to create a sales and marketing network. Many rely on strategic alliances with big pharma to undertake these business functions. Firms also subcontract production capabilities in order to increase their speed to market and to minimize their investment outlays

Summary

The changing paradigm of medical care and drug discovery has created the need to capture even more value along each stage of the value chain. Since a higher return on investment is generated in downstream stages of the value chain, biopharmaceutical companies must develop many different types of technologies in order to maximize their profits. The explosion of alliances between big pharma and small biotech companies demonstrates the primary method by which companies are extending their capabilities along the entire length of the value chain, thus altering the profile of the industry as a whole.

FIGURE 7: DRUG DISCOVERY ACTIVITIES AND TECHNOLOGY UTILIZED



Source: STRATEGIC HEALTH INNOVATIONS, 2000

Technological innovation and revolution are at the core of value creation, from the very earliest stage of disease target identification, through product formulation to market development. For

this reason, it is important to identify the key technological drivers and trends affecting the biopharmaceutical industry.

Part B: Key Technologies and Drivers

This technology overview focuses on technologies that support three areas of the biopharmaceutical value chain:

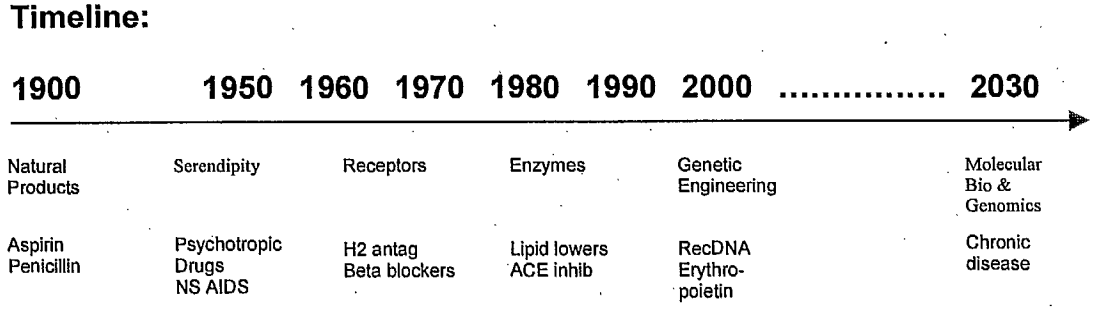
1. **Basic Research**
   a. Genomics, including bioinformatics
   b. Proteomics
2. **Product Development**
   a. Combinatorial Chemistry
   b. Rational Drug Design, including x-ray crystallography
   c. Pharmacogenomics
   d. New Therapeutics, including gene therapy, cell therapy, therapeutic vaccines, phototherapy
3. **Market Development**
   a. Drug Delivery
   b. Diagnostics
   c. Information Technology

While the boundaries between the existing and innovative technology platforms are often fluid, and companies are rarely focused on one platform, STRATEGIC HEALTH INNOVATIONS' focus is on categorizing them according to the stage of the value chain in which the most value is generated. For example, some technologies, such as genomics platforms, are important at the beginning of the value chain for disease target identification. Genomics platforms are then often used in combination with other technologies, such as high throughput screening and bioanalytical software, to enhance the drug targeting and product development process. At the other end of the value chain are products such as needleless technologies that are being developed to aid in marketing and delivering both the new gene and cellular-based drugs that cannot be delivered orally.

2.4 Innovative Technology

Innovation in industries generally occurs through "Schumpeterian discruption" or creative cycles of destruction in which earlier generation technologies are replaced by the next generation technology. Past and current activity in the biopharmaceutical industry, along with future projections, can be charted in such cycles. Beginning with the discovery of natural products at the turn of the century, such as aspirin and penicillin, the pharmaceutical industry has evolved into a $100 billion sector harnessing the latest scientific techniques, many of which are dazzling by lay standards.

FIGURE 8: CYCLES OF INNOVATION IN PHARMACOTHERAPEUTICS



Source: Lehman Brothers Pharmaceutical Research

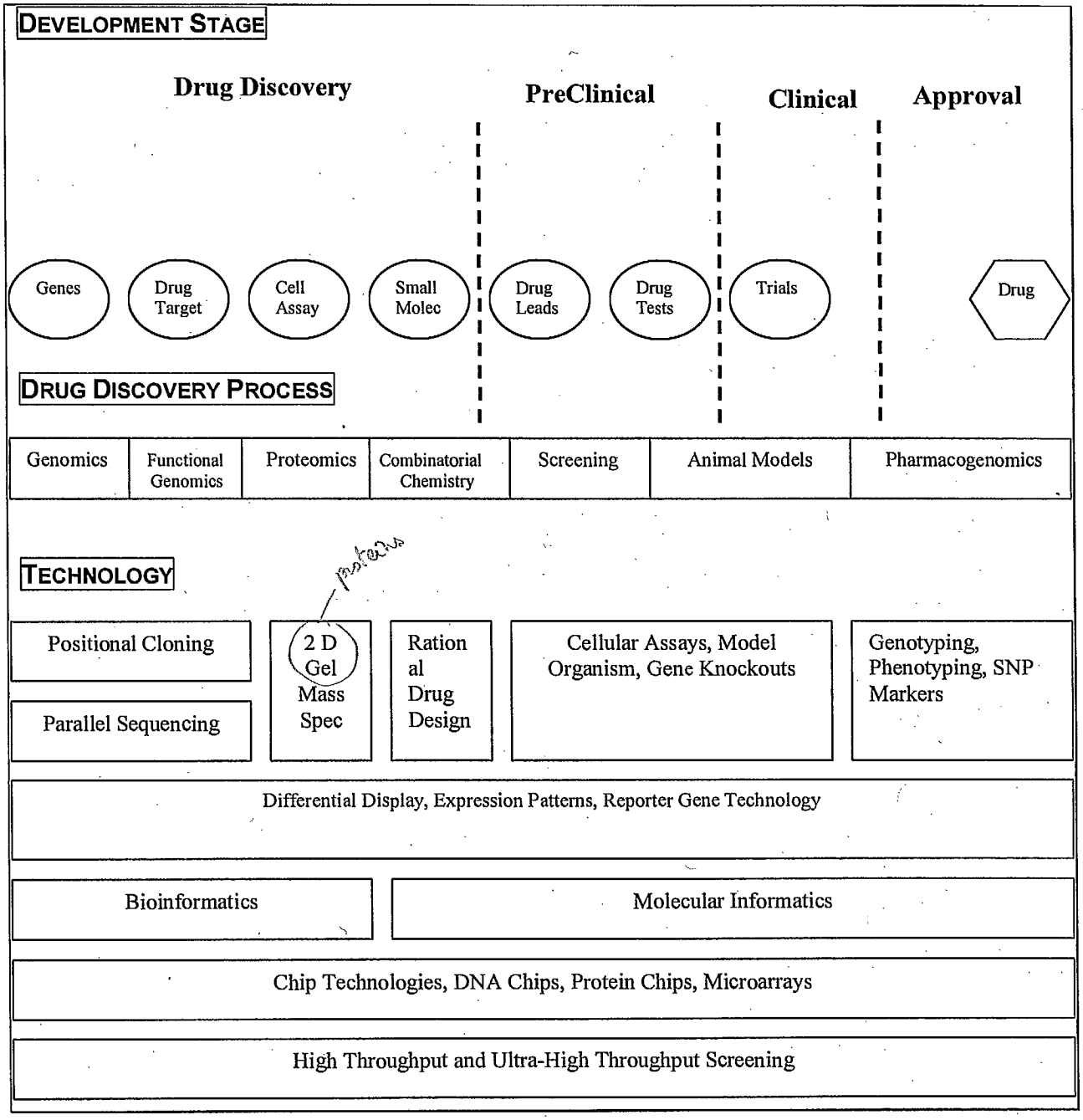
Prior to 1980, the pharmaceutical industry was essentially a fine chemicals business, and the biopharmaceutical industry did not yet exist. Basic research in molecular biology drove the production and development of chemicals of sufficient specificity for use in molecular disease targets.

From the year 2000 to 2010, however, STRATEGIC HEALTH INNOVATIONS predicts that the new technological cycle in the pharmaceutical industry will be focused upon platforms derived from genomics, such as proteomics and pharmacogenomics. Genotypic drug discovery will likely be responsible for fuelling the anticipated steep growth of the biopharmaceutical industry. In the past three years, biotechnology driven developments have introduced almost thirty new biopharmaceuticals in the North American market including:

- The first monoclonal antibody for a type of metastatic breast cancer
- The first recombinant clotting factor for hemophilia B
- The first biologic promoting platelet production in chemotherapy patients
- The first monoclonal antibody against non-Hodgkins lymphoma, a type of cancer
- A genetically engineered injectable for rheumatoid arthritis

The drug development process has become increasingly complex with the constant introduction of new analytic technologies, platforms and research areas. These developments are evidence of the impending explosion of new products spawned from increasing pharma-biotech alliances.

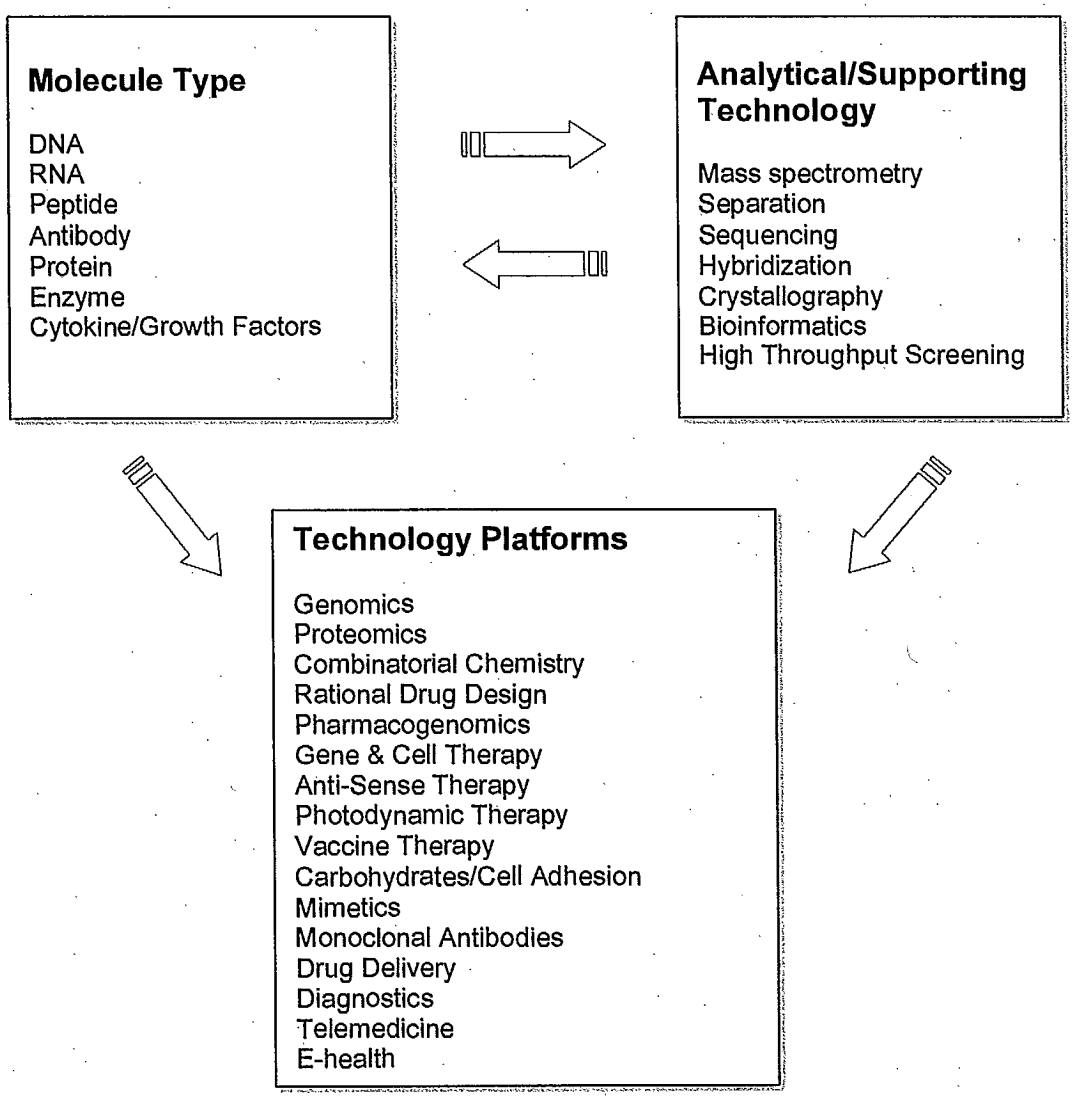
FIGURE 9: THE NEW DRUG DEVELOPMENT PROCESS



Source: Burrill & Company

New technology platforms—defined as drug discovery research areas that give rise to several products, often supported by several analytical technologies—are continually being established. They are founded upon basic scientific research on molecules such as DNA, proteins and antibodies, with the support of physical analytical technologies, including mass spectrometry, PCR, and DNA sequencing.

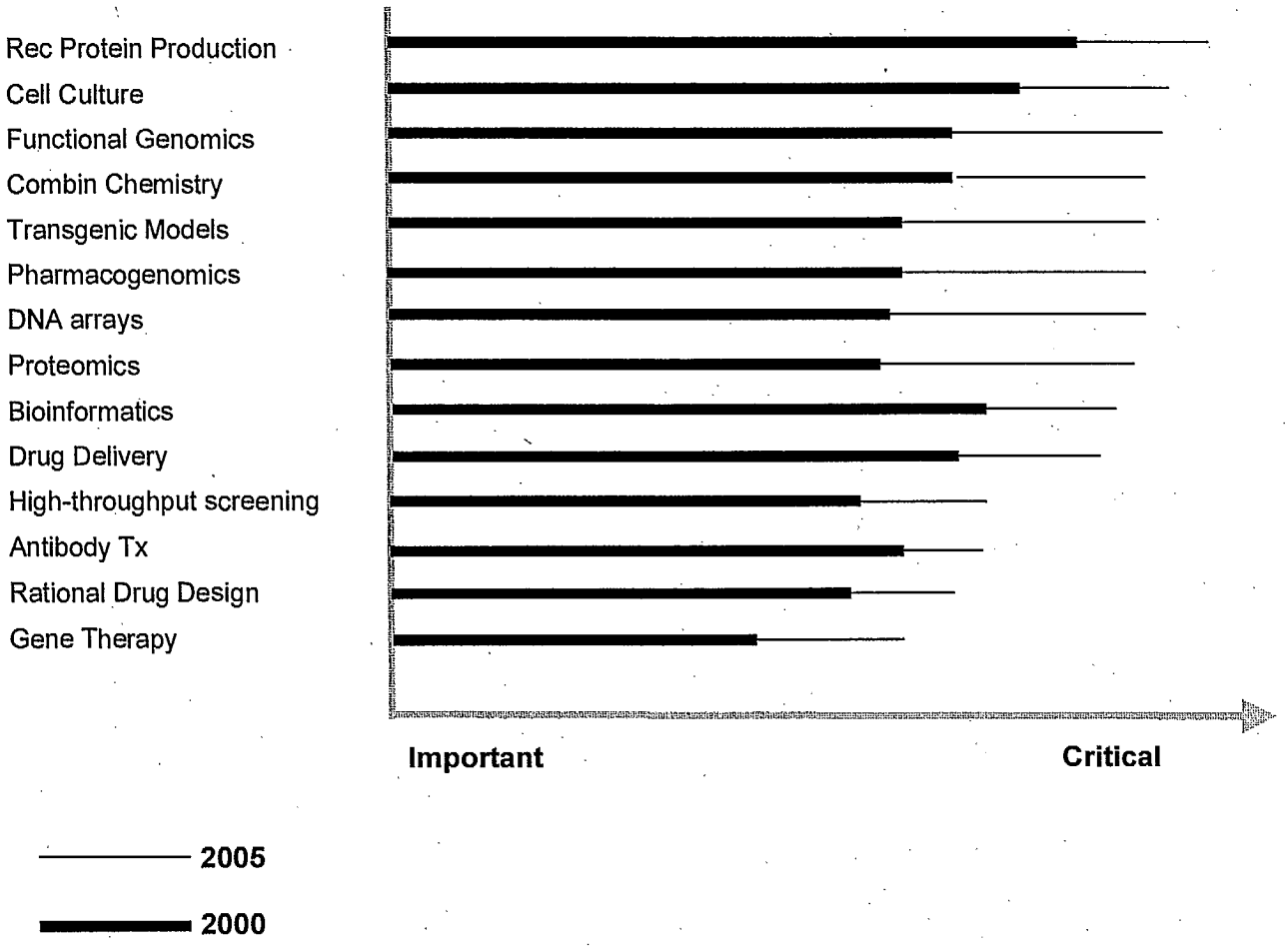
FIGURE 10: TECHNOLOGY PLATFORMS



Source: STRATEGIC HEALTH INNOVATIONS, 2000

In order to identify an increasing number of drug targets, to reduce the time to market and to increase revenues, big pharma is funding much of the basic research pursued in publicly funded government and university laboratories, with a goal of developing commercially viable technology platforms. This overview describes the technology platforms outlined in Figure 8, and provides some detail about their supporting technologies and the future outlook for companies choosing to embrace them. Some of the major platforms and their expected level of importance (from important to critical) at present day and in the year 2005 are presented in Figure 9.

FIGURE 11: TECHNOLOGY FOCUS OF BIG PHARMA



Source: Ernst & Young's European Life Sciences 99 Sixth Annual Report, 1999

2.5 Basic Research: Disease Target Identification

Certainly, at the basic research level, the genomics technology platform has received a great deal of attention. With the identification of several genes for common diseases such as various cancers, Alzheimer's disease, rheumatoid arthritis and diabetes, the search is now directed toward cures for these chronic and degenerative diseases with the help of genomically derived technology platforms. Genetically engineered medicines, in the form of gene therapy or recombinant therapeutic vaccines, hold a real promise for delivering specific and cost-effective treatments. In the immediate to short-term, significant growth is expected in supporting core biopharmaceutical technologies, including bioinformatics, biosensor technology and gene therapy.

A fundamental philosophy of the biomedical sector is that an understanding of the biological pathway that produces disease will lead to innovative biopharmaceutical products to combat disease. The genomics technology platform promises to facilitate the identification of genes, and subsequently their protein units, that play a role in disease, hence providing the key for the development of treatment products.

In this section, two broad categories of technological platforms rooted in basic research (i.e. drug target identification) are discussed:

1. Genomics Technology
2. Proteomics Technology

Genomics Technology Platform

Background

Genomics has contributed to the development of many technology platforms—including proteomics and new therapeutics—that are being developed by biopharmaceutical companies. A genomics technology platform can be defined as one that utilizes analytic technologies, such as sequencing, positional cloning and functional genomic micro-arrays, to understand and characterize the human genome.

The human genome is comprised of 46 chromosomes with more than 100,000 units of heredity (genes) located on them. More than 3,000 diseases are believed to be due to inheritance of single gene mutations.

The anticipated future changes in health care associated with the genomics revolution are often equated with the dramatic way that information technology has changed our world.

The task, or more appropriately the race, to sequence the human genome has been undertaken by the non-profit Human Genome Project, headed by the U.S. National Institutes of Health, and several industrial ventures including Celera Genomics, Incyte Pharmaceuticals, Millennium and

Human Genome Sciences. In March 2000, Celera published the entire genome of the Drosophila fruit fly and in April 2000 announced the complete sequencing of the genome from one human being. The Human Genome Project predicts completion in 2003.

Celera's recent filing of 6,500 new patent applications on genetic molecules at the U.S. Patent Office has created controversy and increased the urgency to examine the ethical and legal issues surrounding gene patenting. There is concern that by patenting the founding technology that gives rise to all the downstream products, there will be monopoly ownership of biopharmaceutical products, and subsequent enormous price inflation. The controversy has been fuelled further by U.S. President Bill Clinton's and British Prime Minister Tony Blair's joint pledge to make gene sequences publicly available. Case studies on the Clinton-Blair Accord and Celera Genomics are available at the end of Chapter 2. Celera Genomics is the company that is considered the international benchmark for commercialization of the human genome and is also the company that has raised the controversy that generated a response from Clinton and Blair.

While genomic science holds great promise, it also raises several issues including:

- The need to map the information provided by DNA sequence data
- Developing biopharmaceuticals of sufficient specificity and selectivity to interact with identified molecular targets
- Ethical and social issues associated with genomic drug discovery and propriety

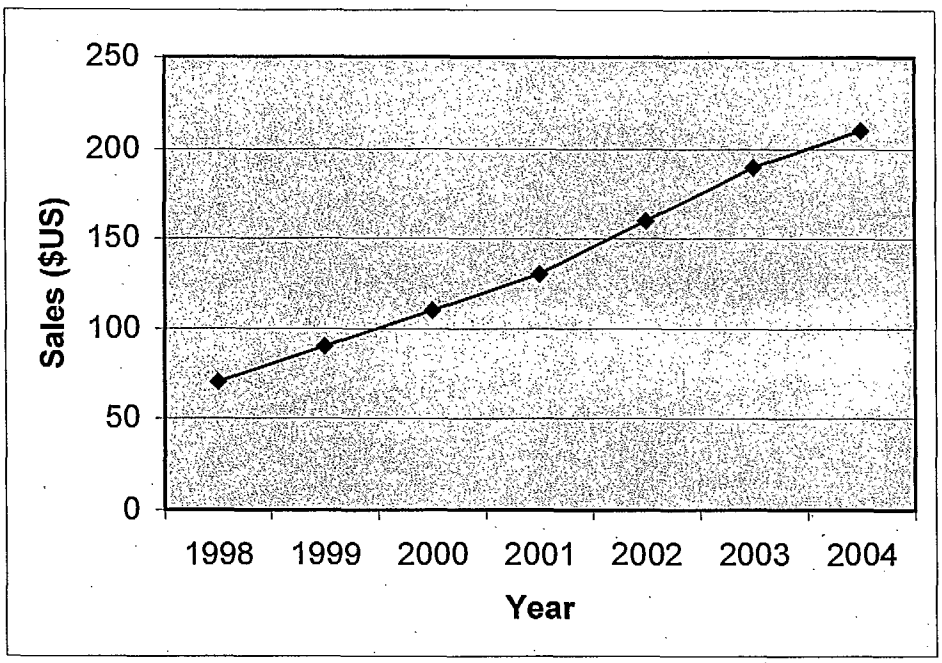
Despite these concerns, there is widespread belief that genomics will be the foundation for drug delivery, health care and the economy of the future.

Technology

Large Scale Sequencing

Typically, companies involved in large scale sequencing compile large databases of genetic sequences. Using technologies such as traditional slab gels, they identify partial expressed sequence tags (ESTs) or automated electrophoretic DNA analyzers that label molecules with fluorescent dyes, then employ laser detection and specialized software to analyze the result.

FIGURE 12: GENE SEQUENCING SOFTWARE SALES



Source: Frost & Sullivan

Positional Cloning

This traditional method of identifying genetic mutations involves initial chromosomal, and then genetic, linkage of DNA markers from families with inherited disease. After linkage is established, techniques such as amplifying, mapping and sequencing with PCR, electrophoretic gels and fluorescent DNA probes, are employed to focus in on the disease gene target. In Canada, major disease genes that have been discovered using positional cloning include cystic fibrosis, BRCA-1, and Alzheimer's disease.

Functional Genomics

An extension of sequencing and a precursor to proteomics, functional genomics is rooted in gene expression data that monitors the presence and abundance of different mRNA species in different cell types, tissues and disease states. Using DNA probe micro-arrays on glass chips, the activity of gene expression on the genomic level is analyzed.

Chip technologies are at the core of all the activities in the drug discovery process, including sequencing and functional genomics. In terms of cost, speed and sensitivity, chips offer tremendous advantages compared to other previous technologies. They are expected to quickly

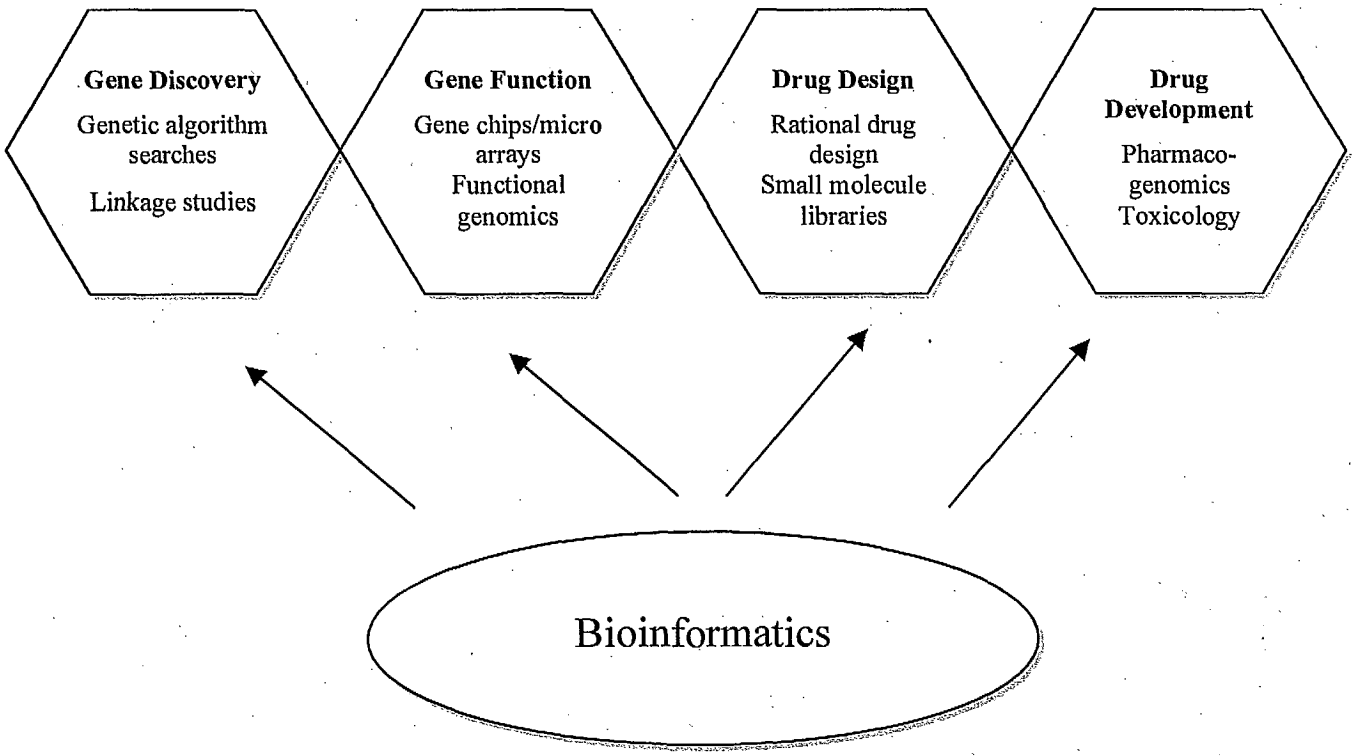
grow into a dominant technology for drug discovery and molecular biology. Two general types of chip technology exist: lab-on-a-chip platforms based in fluid technology and silicon etched channels, and oligonucleotide arrays.

Affymetrix is the most established international biochip company, and is a case study in the creation of strategic alliances to establish brand equity and marketplace leadership. Its GeneChip system is becoming the platform of choice for collecting, analyzing and interpreting genetic information. Affymetrix is involved in many joint programs to develop drug products arising from gene sequencing and expression data. A case study of Affymetrix is available at the end of Chapter 2.

Bioinformatics

Bioinformatics is the use of software tools for data capture, analysis, mining and dissemination. Technically a supporting technology, rather than a technology platform, bioinformatics deserves more extensive elucidation because of its importance to, not just genomics, but many technology platforms throughout the entire value chain. Sales of bioinformatic products are expected to reach $US160 million this year with market potential in five years forecast at $US 2 to 2.5 billion. The figure below demonstrates how bioinformatics underpins the seamless flow of biopharmaceutical innovation from discovery to development.

FIGURE 13: BIOINFORMATICS UNDERLIES THE DRUG DEVELOPMENT PROCESS



Source: STRATEGIC HEALTH INNOVATIONS, 2000

The goal of bioinformatics is to handle the massive volume of data from genomics, high throughput screening, combinatorial chemical synthesis, pharmacogenomics and proteomics, and to subsequently alleviate the bottlenecks in the drug discovery process. This will save biopharmaceutical firms time and money in drug development efforts.

A subcategory of bioinformatics is structural genomics technology that attempts to describe the relationship between DNA sequence and protein structure or function using automation and miniaturization. Software programs predict the protein structure from any DNA sequence and then identify the candidate protein binding regions for drugs. The potential outcome is a highly directed and specific drug with very few side effects. Recent structural genomic initiatives include the June 1999 announcement by the National Institute of General Medical Science (NIGMS) to implement a Protein Structure Initiative described as "an effort designed to organize a cooperative, large-scale effort in the emergent field of structural genomics."

Future Outlook

Genomic data will be especially useful in the development of diagnostics in predicting disease risk by reference to a "normal" genetic sequence. However, this improved diagnostic power does not necessarily translate to an improved ability to manage disease. For example, a risk for Huntington's disease can be accurately determined, but currently there is no treatment available. It is for this reason that the industry has turned to proteomics—or the large-scale analysis of proteins—to further capture value.

Despite the existing limitations and scepticism about the applicability of genomics platforms, the challenge to the Human Genome Project by industrial companies has fuelled widespread industry interest in relevant platforms. Some observers are proclaiming that we are entering the "post-genomic" era of pharmacogenomics, or drug delivery aimed at specific genotypic variations. While the academic community may still be sceptical about the real medical value that has yet to be realized from genome sequencing, it is clear that major pharmaceutical companies are positioning themselves to capture a large portion of the new genomics-driven market. The value of strategic alliances between pharmaceutical and genomic companies was $1 billion in 1998-1999 and is expected to more than double in the next few years (Biovista *Industry Review and Company Database*, 1999).

Celera's corporate growth strategies also deserve some mention in this future outlook because they signal a trend in biotechnology companies worldwide. The company aims to provide services along the entire length of the value chain and along the drug discovery process in order to become a fully integrated biopharmaceutical firm. For example, Celera is concentrating on marketing, not just genetic sequence databases to companies, but also proteomic data and pharmacogenomic markers (in the form of single nucleotide polymorphism or SNP databases). In the value chain, Celera is involved in basic research but is certainly extending its capabilities to product development and market development aimed at consumers. The following is excerpted from www.celera.com:

Consumers

A key goal at Celera is to deepen the amount of genetically related medical information available to individuals. Initially, Celera intends to inform consumers about genomics and better coordinate web-based medical and scientific resources for easier consumer access.

As gene therapies and genetically based drugs become available, Celera will help consumers link back to the information and information tools they need to make informed decisions about their own care.

Ultimately, we plan to become an information resource for anyone interested in the way their unique genetic code determines their disease susceptibility and their reaction to specific drugs.

High Throughput Screening

High throughput screening (also discussed under Combinatorial Chemistry) is highlighted here because the screening technologies are the major reason that genomics and genomics-derived platforms exist. High throughput screening is a general category of analytical technologies including biochips and microarrays (miniaturization), bioinformatics (data management) and bioassays (combinatorial chemistry). The goals of this platform are to:

1. Provide ever-larger compound screening sets
2. Automate systems to screen them even faster
3. Provide an integrated set of equipment and consumables to facilitate the operation

(Source: Theta Reports, 1999)

The world market for high throughput screening techniques was $1.5 billion U.S. in 1998, and is expected to grow by 20% on average, through to $3.3 billion by 2005. At the moment, the market is dominated by Perkin-Elmer and Amersham Pharmacia, but Affymetrix, with 1998 sales of $22 million, is expected to have almost one-third of the market ($1 billion) in the next five years. The market for high throughput is dominated by the United States (60%), Europe (20%) and Japan (17%) (Theta Reports, 1999).

Bioinformatics data is now shifting to the interpretation of information rather than data gathering. However, there are few systems that can handle all of the information during the drug discovery process. Another barrier to widespread integration of bioinformatics is the lack of standards in operating systems. Software that runs on more than one computer platform, or that uses the independent IT platform of Java, will help bioinformatics companies defend their market. Many genomics companies, including Celera, are turning to the Internet as a platform for delivering databases of genetic information.

Proteomics

Definition

Proteomics, or the study of protein pathways that link genes to disease, is the next step in elucidating the human disease profile. About 20% of human genes are active, producing about 15,000 to 20,000 proteins. By determining the profile of these proteins, proteomics—or the protein equivalent of genomics—can help understand the human disease process.

Technology

The field of proteomics has been hampered by a lack of technological innovation, as compared to genomics platforms. Traditionally, proteins were analyzed using laborious techniques such as mass spectrometry and two-dimensional gel electrophoresis. Without the development of a revolutionary methodology equivalent to genomics' polymerase chain reaction, and due to the unwieldy and complex nature of proteins, proteomics platforms in the past could not achieve the scale of precision and productivity that genomics platforms have with PCR and automated sequencers. However, computing power is once again changing the outlook as high-format 2D gels are being developed that can analyze up to 10,000 peptides on a single gel. Software to analyze the ensuing data has also been developed.

Future Outlook

While in 1998, pharmaceutical companies were still trying to capture the value of their investments in genomics companies, 1999 saw the industry turn to processes farther downstream in drug development, including proteomics. With greater buy-in and leaps in development of mass spectrometers and micro-arrays, proteomics databases are the next logical step for genomics companies and "toolbox" companies that leverage their technologies into services and products. For pharmaceutical companies looking to develop fully integrated drug discovery systems, genomics and proteomics, along with their supporting technologies, are important platforms.

Some of the key proteomic events in 1998 and 1999 include:

- Oxford GlycoSciences and Incyte Pharmaceuticals enter into the first international alliance to develop an integrated genomics and proteomics platform; Incyte's first proteomic database was launched in April 1999
- Oxford GlycoSciences enters into a $50 million agreement with Pfizer to identify protein markers for Alzheimer's disease
- Myriad Genetics and Curagen jointly develop a protein interaction map
- Perkin Elmer buys PerSeptive Biosystems, a manufacturer of mass spectrometers and forms a Proteomic Research Center in March 2000
- In June 1999, Amersham Pharmacia Biotech signed two major new deals with Proteometrics LLC and Scientific Analysis Instruments Ltd. that promise to transform the global protein mass spectrometry market
- MDS Inc. launches MDS Proteomics with an $82.5 million private placement

While there is still scepticism that proteomics is the platform from which to generate multiple drug hits, it is on its way to becoming an integral platform for any company involved in drug discovery.

2.6 Product Development I: Lead Target Identification

While basic research focuses on drug target identification, product development involves identifying drug leads, developing them into tests and then administering them in clinical trials to test for efficacy and dosage. The next stage of the value chain—market development—occurs once the drug has been approved.

Combinatorial Chemistry

Definition and Technology

Combinatorial chemistry is the rapid synthesis of a larger number of compounds that are comprised of smaller molecules, such as peptides, organic molecules and sugars. The synthesis creates a "chemical library" that can later be used to find a drug target.
Libraries can be of two types: lead generators that have large compounds with diverse structures, and an optimizer library that has smaller compounds with narrow structures.

After the compounds are synthesized, they are screened using high throughput methods (i.e. bioassays). The data must also be collected using bioinformatics software packages, and then managed to generate small molecule drug leads.

Future Outlook

Chemical libraries are generally supplied by dedicated biotechnology firms with small biopharmaceutical firms licensing the technology to gain access to specific libraries. Big pharma, however, are developing their own combinatorial systems as part of their overall strategy to integrate all aspects of the drug development process. The underlying technologies of combinatorial synthesis—high throughput screening and bioinformatics—are expected to be the dominant technologies over the next five years.

Rational Drug Design

Definition and Technology

Rational drug design involves the use of X-ray crystallography that determines the three dimensional structure of proteins for a better understanding of disease targets. It facilitates the design of specific drugs with the proper shape and distribution of atoms to bind tightly within key sites of the target protein and thereby block its biological action. HIV, cancer, and inflammatory and autoimmune diseases are all good candidates for this approach. To date, most drugs have been made by tedious trial-and-error methods which generated compounds that may not have a higher affinity for their target. Alternatively, drugs utilizing rational drug design will be more receptor-specific and therefore produce fewer side effects. X-ray crystallography is the

only technique currently available that allows scientists to see complicated structures at the atomic level.

Future Outlook

Applications of this technology are limited by the availability of crystals of the target protein. Growing crystals in the gravity free environment of space holds the promise of a supply of larger and higher quality crystals. Some of the space-grown crystals which have provided important drug design data include Factor D, a plasma protein formed as a result of complications from open heart surgery, heart attacks, and strokes; Neuraminidase, occurring on the surface of the influenza virus for treatment of the flu; and recombinant human insulin. The renewed interest in rational drug design arises from the ability to use bioinformatics to create a drug template for use in pre-screening combinatorial libraries.

2.7 Product Development II: Clinical Development

Pharmacogenomics

Definition

Other promising models of drug delivery include the pharmacogenomics model of predicting drug participation based on genotype. Drugs that are highly effective in some people may be lethal in others. Pharmacogenomics attempts to reduce mortality and morbidity by determining the correlations between drug responsiveness and the genetic profile of the patients. The analysis of single nucleotide polymorphisms (SNPs) that represent genetic variation in a population has been a focus of research. SNPs can be "tags" for potential genotype-based drug targets. DNA chip technology will be instrumental in rapid genotyping of individuals to determine variability in drug metabolizing genes and to determine differential expression of genes in response to a drug.

Theoretically, pharmacogenomics will reduce the cost of clinical trials and general health care expenditures as consumers receive targeted drugs. While critics believe that the promise of pharmacogenomics will not be realized due to insurance issues and the resulting segmentation of the pharmaceutical industry, other industry observers believe that the era of "blockbuster" drugs is gone, and that tailored drugs will be an eventuality (Boston Consulting Group, *The Pharmaceutical Industry Into Its Second Century*, 1999).

Technology

DNA arrays, or chips, open the possibilities for "massively parallel solid phase cloning" that can allow an enormous number of genes to be analyzed simultaneously. These high throughput automated systems can identify targets in cancer, central nervous system, cardiovascular and infectious disease. Diagnostic applications to allow detection of disease related to gene sequence variation are currently the major thrust of biochips. Commercial systems are already on the market including a cytochrome P450 gene chip that identifies potential poor drug respondents. It

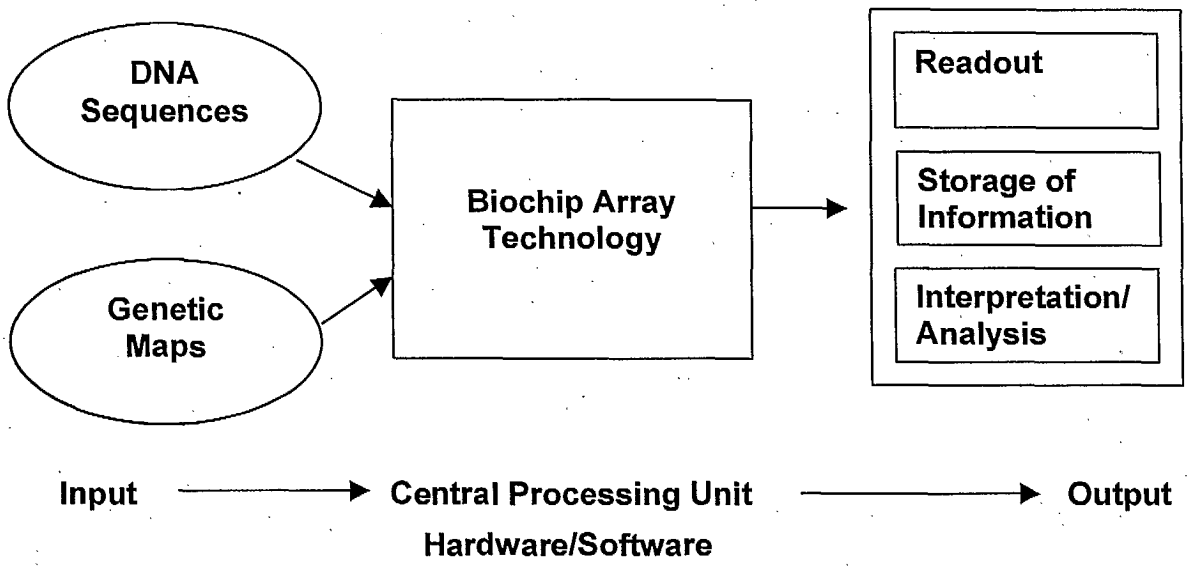
is believed that the technology already exists for routine clinical analysis using DNA chips and a single drop of blood.

The manufacturing technology involved in DNA chip production is the same as used by microprocessor manufacturers: photolithography on silicon. Micro-miniaturization of chips has taken place in tandem with drug discovery needs of high-throughput analysis. Surface micro-arrays (gene chips) have been designed with tens of thousands of reaction zones onto which DNA specimens can be deposited. This may conceivably culminate in the development of nanochips built from individual atoms and self-assembling molecular structures such as lipid tubules. The ultimate goal is a fully integrated analytical system, or a "lab on a chip". Chips that currently exist are capable of sample preparation, detection and analysis, while experimental models of chips with heaters, valves, pumps, microfluidic controllers, and electrochemical and electroluminescent detectors have already been built.

Future Outlook

Moore's law predicts that computer chip power doubles every eighteen months, also appears to apply to DNA chips. It is expected that the raw analytical power to scan an entire genome for malfunctioning genes could soon be available on a single chip. Pharmacogenomic data is extremely useful because it may significantly reduce the cost of clinical trials by pre-determining and excluding the particular subset of the population who are likely not to respond. This will result in more targeted drugs that are cheaper to develop.

FIGURE 14: BIOCHIPS ARE AN INTEGRATED OFFERING OF SEVERAL TECHNOLOGY PLATFORMS



Source: Ernst & Young European Life Sciences 99 Sixth Annual Report, 1999 and STRATEGIC HEALTH INNOVATIONS, 2000

Biochip technology involves integrating a number of core technologies, including information technology hardware and software. The successful development of such technology would clearly require expertise beyond the realm of a single biopharmaceutical company.

However, in trying to capture the value that is created in owning a SNP, small biopharmaceutical companies have started to patent SNPs successfully while major pharmaceutical companies established a non-profit SNP consortium with funding from the Wellcome Trust. The goal of the consortium is to establish an SNP map that would be publicly available to researchers and corporations, and that would become the generally accepted standard by which the FDA would approve pharmacogenomic drugs. Another consortium goal is to avoid the quasi-monopoly situation that could result from ownership of pharmacogenomic data from the proprietary gene sequence databases of Celera, Incyte, and Millennium.

Pharmacogenomics as a concept has the potential to fragment the health care market because it would narrow the market opportunities for existing and future drugs. It also raises issues of genetic privacy and discrimination, by employers, insurers and other stakeholders, based on genotype.

Some key pharmacogenomic events include:

- Establishment of an international SNP consortium by Wellcome Trust and pharmaceutical partners (case study at end of Chapter 2)
- Establishment of companies, including Genaissance Pharmaceuticals and Variagenics, based on the pharmacogenomic concept
- Alliances between diaDexus, SmithKline Beecham and Incyte
- Collaboration between Genset and Abbott
- Formation of a new subsidiary, Millennium Predictive Medicine, by Millennium Pharmaceuticals aimed at pharmacogenomics
- First pharmacogenomic products including Herceptin, designed to treat breast cancer in women with the HER2 genotype; Herceptin is being marketed at $19,000 per treatment, twice the price of Taxol

While STRATEGIC HEALTH INNOVATIONS predicts that pharmacogenomics will be one of, if not the, most important technological platform over the next 5 to 10 years, there are other market factors, such as regulatory, competitive and societal issues, that may marginalize or slow down the pace of advancement of the platform.

New Therapeutics

The innovative therapeutics that the biopharmaceutical sector is focusing on include:

- Gene therapy
- Cellular therapy
- Other innovative therapies: anti-sense, phototherapy, recombinant DNA, and monoclonal antibody therapy

Gene Therapy

Definition and Technology

Gene therapy is the introduction of genetic material (DNA or RNA) into cells expressing a genetic defect. The goal is to alleviate or cure the disease by introducing a "normal" copy of the malfunctioning gene into the cell in order to stimulate proper or "normal" functioning. A decade ago, the first gene therapy procedure was carried out in a patient with severe adenosine deaminase (ADA) immunodeficiency syndrome. A normal ADA gene was successfully introduced into patient's diseased RNA and provoked an encouraging immune participation. Approximately 3,000 people worldwide have been treated with gene therapy, although, to date, no gene therapy has been completely effective in curing disease. Interest has resurged in gene therapy due to the genomics revolution. Although applications for cancer remain the focus of gene therapy research, new disease applications are being explored, including neurodegenerative disorders, immunology and trauma.

Popular therapeutic approaches include anti-sense therapy that uses the mirror images of molecules to interfere with genes. Anti-sense synthetic reagents bind to defective genes and halt

the production of inappropriate proteins. Currently, the main obstacle lies in delivering the therapeutic DNA into the cell. Viral vectors are the main source of delivery platforms since viruses naturally seek out target cells to which they deliver their genome. The ordinarily infectious virus is attenuated by deleting much of its natural genetic material. However, cells are very good at defending against viral vectors, and typically reject the introduced vector. Alternatively, liposomes or electroporation methods that open pores in the cell membrane to allow the introduction of a gene therapy may be utilized to deliver the new gene.

Future Outlook

Gene therapy is potentially a prominent therapy of the future, especially if delivery issues can be resolved. Due to regulatory and safety issues, the routine use of gene therapy is not expected until 2005. Most major pharmaceutical and biopharmaceutical companies are engaged in gene therapy development. Some of the recent advances in gene therapy include:

- Cancer: clinical trials are underway for gene therapies for melanoma, breast cancer, ovarian cancer, and chronic myelogenous leukemia
- Apoptosis: Genta Inc. is developing a broad therapeutic approach to restore the sensitivity of cells to apoptosis
- Asthma: Affymetrix has a collaboration with Progenitor Inc. to identify asthma polymorphisms and therapies
- Cardiovascular disease: several initiatives are ongoing including clinical trials for angiogenic gene therapy; a discovery of a high density lipoprotein regulatory gene, identification of 80% of the genes active in the cardiovascular system by a team from University of Toronto and Asia; and clinical trials for vascular endothelilal growth factor (VEGF) therapy

It is difficult to quantify the market for gene therapy products since they have not been used outside of clinical trials. Theta estimates that within the next two years, the market could be $1 billion (Theta Reports, 1999).

Cellular Therapy

Definition and Technology

Cell therapy is the employment of particular cells, such as stem cells, to treat damaged organs. The cells can be obtained either from the patient or from a donor. Typically, the cells are extracted from bone marrow, embryonic or umbilical cord blood cells and injected into the bloodstream, where they divide and grow into blood and immune cells that can correct the existing genetic deficiency.

Once harvested, the cells could be genetically modified or used as is. The controversy around cell therapy lies in the source of cells. The use of embryonic or umbilical cord blood cells has generated public controversy, although the recent discoveries of adult stem cells in bone marrow may serve to mitigate the controversy. Stem cells have been found to form many different types of tissues, including muscle, connective tissue, bone and possibly spinal and brain tissue. In

September 1999, the FDA approved the first clinical trial for cell therapy for spinal cord regeneration by Proneuron Biotechnologies Inc.

The Future Outlook

As with gene therapy, cell therapy is being performed by many biopharmaceutical companies. Some recent events in cell therapy include:

- Genzyme's preclinical studies on cell therapy for cardiovascular disease, conducted jointly with Toronto General Hospital, which look extremely promising
- Titan Pharmaceuticals' cell therapy for Parkinson's disease which is efficacious in primate studies
- Aastrom Biosciences who have received three patents on two novel technologies for cell therapy and a core patent for a cell therapy system

In 1998, approximately 50,000 cell therapy procedures were performed worldwide. It is expected that this number will more than double over the next 5 years to 110,000. The main market for cell replacement therapy is the United States, with 60% of procedures performed there (Theta Reports, 1999).

Photodynamic Therapy

Photodynamic therapy is based upon the action of light on specific chemicals called photosensitizers or porphyrin-type compounds. Such chemicals are able to accumulate in target tissues such as rapidly growing cancer cells.

When illuminated by light of a specific wavelength, a photochemical reaction releases energy, converting normal oxygen into a highly reactive form capable of destroying diseased cells. Other parts of the human body are unaffected both because they have not accumulated the photosensitizer and because they are not selectively illuminated. Photosensitizers have no toxicity in the absence of light. The significant benefit of phototherapeutics is that the therapy can be applied on an outpatient basis, its side effects being relatively benign.

To date, only one photosensitizer, Photfrin (a mixture of oligomers of hematoporphyrin) marketed by QLT Phototherapeutics for esophagaeal cancer, has been approved for treatment. QLT Phototherapeutics is profiled as a case study of a successful Canadian company in this niche field that now has a market capitalization of $6 billion.

Second generation photosensitizers are being developed that are receptive to longer wavelengths of light that can penetrate deeper into tissues. Research is currently underway with bacteriochlorophyll that produces reactive molecules at near-infrared light and may hold promise of being a third-generation photosensitizer.

Carbohydrate Based Therapies
Since the launch of the widely used anti-coagulant and carbohydrate-based drug, Heparin, there have been several new glycobiologic drugs, most recently Relenza (made by Biota/Glaxo for influenza). Glycotherapeutics or carbohydrate therapies are based on the interaction between carbohydrates that regulate function and bind small molecules on cell surfaces. Carbohydrates are promising as drug targets. However, their complex nature makes it difficult to isolate single isomers. For this reason, glycotherapeutics has lagged behind protein-based platforms.

There are now over 40 companies worldwide involved in glycobiology including a number of Canadian companies indicated by an asterix:

- GlycoDesign*
- Biomira*
- Texas Biotech
- Synsorb Biotech*
- Bayer
- Abbott
- Oxford GlycoSciences
- Glaxo Wellcome
- Gilead/Roche
- Biocryst/Johnson & Johnson

These companies are developing technologies involving the binding of enzymes (glycosyl transferases) or enzyme inhibitors to complex sugar molecules in order to inhibit or facilitate molecule interaction. A case study of Glycodesign, an innovative Canadian company, is available at the end of Chapter 2.

Mimetics
Mimetics are chemically modified compounds that mimic the action of naturally occurring biomolecules and can exhibit enhanced drug function. Mimetics are fragments of large proteins, natural peptides, synthesized small protein fragments or organic small molecules that are used to "mimic" the activity of large, complex proteins. The first non-peptide mimetic for a large protein was GCSF mimetic, discovered in 1998 by Ligand Pharmaceuticals.

New Vaccine Therapies
In order to counter the pathogenic effects of live attenuated vaccines, the need for multiple boosters of inactivated vaccines, and the ineffectiveness of purified antigen vaccines, new vaccine strategies are constantly being developed. They include:

- Recombinant antigen vaccines that are genetically engineered for antigen production in bacteria or yeast
- Synthetic peptides that can imitate the antigen epitopic surface

- Recombinant vector vaccines that use attenuated viruses or recombinant antigen vaccines to express gene products
- DNA and RNA vaccines that are developed from DNA and RNA fragments which are more stable, cheaper and less risky than conventional vaccines made from disease-causing organisms

It is estimated that over the next 20 years, there will be 20 to 30 new vaccines available with a doubling of the worldwide market from $US 5 billion in 1998 to $US 10 billion in 2003. Therapeutic vaccines are still in development, however, it is believed that the market will reach $950 million over the next two years (Theta Reports, 1999). BioChem Pharma is an example of a very successful Canadian company that found a niche in developing anti-retroviral therapies for HIV and then expanding their capabilities to other markets. A profile of BioChem Pharma is available at the end of Chapter 2..

Monoclonal Antibodies

Antibodies are proving to be the new "hit" in recent drug discovery. Monoclonal antibodies (MAb) were first introduced in the 1970s and are starting to regain their popularity with the approval over the last 2 years of several new products. Antibodies are carriers for cytotoxic drugs, or can be therapies in themselves by binding with therapeutic targets. Some of the recent approvals for monoclonals include:

- Genentech's Herceptin MAb that was launched in 1998 in conjunction with HER2 diagnostic screening to prove the first example of a pharmacogenomic drug; sales are forecasted to exceed $800 million annually
- Idec/Genentech launched Rituxan in 1998, a MAb for non-Hodgkin's lymphoma, sold $73 million in its first six months on the market.
- Zenapax, an antibody that prevents kidney transplant rejection, was launched by Protein Design Labs
- MedImmune's Synagis was approved for treatment of respiratory syncytial disease in infants and children
- Remicade, an antibody therapy for Crohn's disease developed by Centocor, was also recently approved

The therapeutic monoclonal antibody revenues for the international market are expected to grow from an estimated $499 million in 1998 to $4.4 billion by 2008 (Decision Resources, 2000).

Angiogenesis

Angiogenic therapy stimulates the endothelial cells that line arteries to form new blood vessels. Angiogenic inhibition is geared to inhibit vesicular growth, and to reduce metastases in cancer. In 1998, angiogenesis inhibition received a great deal of attention with the sudden surge in media and investor interest in Entremed, a company whose anti-angiogenesis compounds in preclinical development were touted by the *New York Times* as being a cure for cancer. Entremed gained

and lost several hundred million dollars in market capitalization in a single day. However, since then, three of Entremed's compounds have been approved for clinical trials and the company's capitalization has been on an exponential rise, reflecting investor confidence in anti-angiogenic compounds.

Transgenic Models and Cloning

Several developments in cloning technology—such as the cloning of the sheep Dolly in 1997 and of a mouse in 1998—have caught the attention of the public. The pragmatic applications of transgenic models include growing organs for *in vitro* transplantation, or for "workhorse" organisms in clinical research. Other more innovative uses for transgenic animals include the production of protein therapies. Some examples of recent uses for transgenic models include:

- This year Genzyme announced positive results from a Phase III trial of an anti-clotting protein derived from the milk of a transgenic goat
- PPL Therapeutics in the United Kingdom is experimenting with transgenic sheep's milk to produce protein drugs for cystic fibrosis and hemophilia
- Pharming NV, a biotech firm in the Netherlands, is testing whether transgenic rabbits, cows and mice can produce a variety of human proteins for stomach ailments and other bleeding disorders (www.sfgate.com, January 2000)

2.8 Market Development: Drug Delivery, Diagnostics and Information Technology

At this stage of the value chain, a drug product has been approved for launch and is ready to be marketed. However, there are several factors that can affect a biopharmaceutical product's success. For example, a safe, non-invasive *in vitro* diagnostic test that is available over the counter can increase drug compliance.

As well, the explosion of information technology has given consumers access to a wealth of medical and drug information previously unavailable; and medicine is becoming increasingly decentralized. In order to develop fully integrated drug provideres and remain competitive, biopharmaceutical companies will have to integreate technology into their development, sales and marketing processes.

This overview of technologies in the Marketing Development stage of the value chain examines:

1. Drug Delivery
2. Diagnostics
3. Information Technology

Drug Delivery

Technology

Biopharmaceuticals need to be delivered in an active form to their target, and require underlying biophysical technology platforms for successful therapeutic action. Traditional pharmaceuticals, being small chemical entities, have been delivered mostly orally, but this is unsuitable for many biopharmaceuticals.

New biopharmaceuticals, such as recombinant proteins and peptides, are macromolecules that present new challenges for delivery. The oral route makes the therapeutic susceptible to digestion; the skin presents even more of a boundary than the intestine; and transdermal delivery using patch technology has not been very successful. High-pressure needleless injection devices can be used to inject biopharmaceuticals through the skin but this approach have not yet proven popular. New genetic, cellular and protein therapies can also require multiple injections on a daily basis.

A partial list of the potential drug delivery technologies includes:

- Oral gel preparations
- Aerosols
- Chewing gum
- Electroporation therapy that uses pulses to open cell membranes
- Silicon chips that release stored compounds
- Ultrasound devices for therapy
- Transdermal patches
- Microscopic needles
- Liposomes that can transport molecules intracellularly

A traditional approach for non-invasive delivery is via inhalation; this route holds significant promise for biopharmaceuticals. Some benefits include:

- A reduction in total body dose (which also reduces side effects) because the product is not degraded as extensively as per oral administration
- Faster and higher absorption
- Higher bioavailability

Other techniques for drug delivery include dry powder aerosol, and liquid and hydrofluorocarbon propellant. Dry powder aerosols are highly soluble and stable, yet face challenges of moisture control and clumping of powder. Liquid systems are easy to fill yet present challenges of stability and reduced drug payload capacity. Propellant systems (used by asthmatics in metered dose inhalers) are not amenable to macromolecular biopharmaceuticals.

New technology has been developed that uses sonic velocity compressed air to aerosolize the powder, requiring that the patient inhale in one slow breath. Immediate opportunities being explored for this technology include heparin for blood clotting problems, human insulin for diabetes, alpha 1 antitrypsin for emphysema and cystic fibrosis, interferons for hepatitis B and C and calcitonin for osteoporosis.

Ultimately, it is conceivable that an implantable microchip controlled by a miniature computer would be capable of variable dosage release of multiple biopharmaceuticals over a lengthy period. These implantable delivery systems would be tiny silicon chips encased in a semi-permeable membrane, potentially controlled by remote control through the skin.

Future Outlook

Sales of drugs associated with novel delivery systems are predicted to grow from $US 10 billion in 1998 to $US 30 billion by 2007. The total market for drug delivery is expected to triple to $77.6 billion by 2005, from $27 billion in 1998 (Theta Reports).

TABLE 8: SALES DISTRIBUTION OF DRUG DELIVERY PRODUCTS 1996

Delivery Mechanism	Percent of Market
Oral controlled release	53
Inhalation	27
Implant	10
Transdermal	8
Other	2
Total	**100 ($US 11.5B)**

Source: Dillon Read Equity Research

Alternative drug delivery technologies comprise one of the fastest growing market segments in biopharmaceuticals. Over the next 5 to 10 years, development of oral drugs will dominate the market as other technologies must await proof of their safety. Oral drugs will be formulated to be active for periods as long as one month. Aerosol technology will experience moderate growth, and transdermal patches and gels will experience the largest growth as newer products are targeted at therapeutic areas such as diabetes, Alzheimer disease, depression, and asthma.

Diagnostics

Technology

As the consumer health care market changes, POC (point-of-care) tests are increasingly used as quick, private and convenient ways of detecting disease. Examples of some technologies and tests include:

- A workplace breast cancer screening project undertaken by Zeneca Inc. that saved the company $1.1 million in direct costs
- Urine-based assays that are being developed for sexually transmitted diseases, and saliva-based tests for HIV, hormones and drugs
- The first over-the-counter test for drugs-of-abuse, Quick Screen At Home Drug Test, was cleared for approval by the FDA

Generally, there are two areas that are being developed in diagnostics:

1. Sampling alternatives to traditional blood sampling
2. Miniaturization technologies

Sampling alternatives are non-blood samples using urine, saliva, sweat or hair. Some examples of tests being developed are listed below:

TABLE 9: SAMPLING ALTERNATIVES

Company	Test	Sample	Status
Americare Biologicals	HIV 1,2	Saliva	Market
Avitar	Drugs-of-abuse	Saliva	Market
Beacon Diagnostics	Cancer	Saliva	Development
Biex	Estriol	Saliva	Market
Bion Medical Sciences	Bladder cancer	Urine	Market
Calypte	HIV 1	Urine	Market
Cortecs	H. pylori	Saliva	Market
IMI	Cholesterol	Skin	Development
Oncor	Lung cancer	Saliva	Development
OsmeTec	Infections	Gases	Development
Pacific Biometrics	Osteoporosis	Sweat	Development
SpiraMed	Metabolic disease	Breath	Development
TCPI	UTI proteins	Urine	Market

Source: Theta Reports, 1999

Miniaturization or nanotechnology is also being emphasized for the development of laboratory tests, the best known of which is glucose self-monitoring. Gene chip technology has contributed to the interest in miniaturizing clinical tests. Companies such as Affymetrix have already marketed clinical diagnostic test products based upon chip technology (HIV GeneChip). The use

of miniaturized *in vitro* diagnostic systems is not expected to become a clinical routine for several years. The market for miniaturized tests performed by health care professionals is estimated at $2 billion and is expected to grow 10% to 15% annually (Theta Reports, 1999).

Information Technology

The advent of telephone hotlines and the Internet has challenged the way medical care is delivered simply because consumers are increasingly taking their health into their own hands. The perception of the consumer's new role is summarized by Jan Leschley, CEO of SmithKline Beecham: "We need to throw out the old health care delivery system and accept that the consumer, the patient, is king—and we better [sic] service the king." E-business has become the medium for pharmaceutical companies to deliver new products and services aimed at the consumer. E-business offers the following advantages to biopharmaceutical companies:

- Use of web-based technologies to deliver consumer service tools, e.g. help lines and access to clinical trial data
- Collection of information from websites to generate more sales and to understand customer needs
- Building consumer loyalty by creating a community around specific diseases and disorders
- Recruitment for clinical trials, reducing development time and costs due to higher success rates; this, however, will increase the near-term demand for patients and investigators

Some of the existing cyber health ventures and trends include:

- Prudential Health Care's asthma management program is online at www.prudential.com
- Home Access Health Corporation delivers its HIV home counselling and testing services over the Internet
- Orchid Biocomputers plans to delivery direct-to-consumer single nucleotide polymorphism (SNP) analysis using an "SNP" of the month marketing plan
- Consumer health channels such as DrKoop.com offer medical information databases and interactive tools
- GeneLink provides an online DNA collection kit that allows families to collect and preserve their DNA
- Quintiles offers access to clinical trials through several sites
- WebMD uses the Internet as a tool for customers to track their disease symptoms and interact with physicians
- Planet Rx delivers on-line medical prescriptions, drugs and advice, practices which have stirred controversy in the medical community

Clearly, health care's future will involve the Internet and other information technologies as a decentralized health care system with enfranchised consumers evolves.

2.9 Summary

Technology Trends

The genomics platform has entered a stage of maturity, and companies are now turning to other technologies to try to create even more value from sequencing the human genome. Genotypic drug discovery is also currently facing challenges, including the management of information provided by DNA sequencing data. Bioinformatics is evolving to deal with complex multivariate analysis of gene expression based upon multiform mRNA. Once bioinformatics demonstrates gene function in response to varied stimuli, the challenge will then be to position specific gene products within various cellular pathways and then to validate these as drug discovery targets. Some approaches here include the use of gene-knockout methods and anti-sense drugs.

With the availability of rapid throughput methods for the synthesis and testing of anti-sense agents coupled to automated reverse-transcriptase PCR methods, anti-sense intervention can be used as a powerful tool in functional genomics. This will validate the gene product identified as a therapeutic target. However, the decision to invest in a biopharmaceutical program focused on a specific target identified through functional genomics is fraught with high risk simply because there are many more targets about which less is known. This will require a portfolio approach focused on different potential opportunities.

The next challenge in the current genomic age is developing biopharmaceuticals of sufficient specificity and selectivity to interact with identified molecular targets. New technologies, such as rational drug design and combinatorial chemistry, are now overcoming some of these difficulties. In addition, monoclonal antibodies, gene therapy, and anti-sense technology also have a role to play in increasing specificity of drug design.

These new genomic-based technologies promise a more streamlined and effective clinical trial process that will shorten the time to market and improve bottom line results in profitability. They also give rise to societal and consumer issues such as whether the market and industry are ready for "personalized medicine", and whether society will reject genomic medicine due to the ethical issues involved.

Industry Trends

In summary, the biopharmaceutical industry's future outlook is still technology-driven. Rapid changes in technology are paving the way for a revolution in medicine. In the early beginnings of biopharmaceutical development, companies were formed around individual researchers with therapeutic specialties. Big pharmaceutical companies have changed the competitive landscape

by charging to the forefront of biotechnology advancement. Massive companies with economies of scale and scope are leading the biopharmaceutical revolution by investing in technology platforms of smaller companies.

Pharmaceutical companies are acquiring knowledge rapidly through strategic alliances and acquisitions of biotechnology companies. Novartis is an example of a company, however, that is integrating the entire drug discovery system through a $250 million institute in San Diego.

While there are very few companies with the scale of Celera Genomics, many companies are positioning themselves similarly—as service providers to pharmaceutical firms, with an ultimate goal of becoming a pharmaceutical company itself. Other areas of medicine and technology are also rapidly converging. Bioinformatic information technology platforms are accelerating the pace of drug target discovery, the Internet is decreasing the time for clinical trial development, and biochips are revolutionizing drug delivery. The next five to ten years in biopharmaceuticals promises to be an exciting time as technological drivers constantly shift and, more importantly, accelerate the drug development process.

Case Studies

Case Study: The Clinton-Blair Accord
Joint US/UK Statement on Access to Sequencing Data from Human Genome Projects

On March 16, 2000, United States President Bill Clinton and UK Prime Minister Tony Blair issued a joint statement regarding the disclosure of raw data from ongoing human genome sequencing projects. President Clinton stated that, "To realize the full promise of this research, raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere." He also stated that, "Intellectual property protection (i.e., patents) for gene-based inventions will play an important role in stimulating the development of important new health care products."

The statement came a week after secret partnership talks between the Human Genome Project (HGP), a US and UK publicly funded, multinational research project, and Celera Genomics (CG), a private US company, broke down over the issue of public access to shared data. Both groups have concurrently been attempting to locate and sequence all of the genes in the human genome. Both have also previously stated that they intend to make their raw sequencing data freely available to the public. The HGP has been making the data available though the Internet on a daily basis for researchers to use without conditions. CG intends to recoup costs by encouraging researchers to subscribe to their genomic databases, utilize additional information regarding the sequences that CG has amassed, and to use their proprietary software tools and powerful computers for research. CG, as well as a number of other genomics based companies, has publicly welcomed the statement.

The statement has been seen by many as a direct result of private companies holding back their sequencing data until their filed patents are formalized. In October 1999, CG filed provisional patents on approximately 6500 genes discovered in their first billion sequenced bases of DNA. The post-statement emphasis from the White House concentrated on encouraging companies to release their DNA sequence information as soon as possible and ensuring that intellectual property law and patenting would continue unchanged for products derived from these genes.

However, skittish investors have interpreted the statement as a direct refutation of the ability of biotech companies to patent their gene discoveries and the products derived from them. This interpretation lead to large losses in the stock values of genomics and biotech companies. The Nasdaq dropped 28% in a one day period due to this sell-off. The US Patent and Trademark Office (PTO) immediately announced that the statement in fact reaffirmed that US patent policy remained unchanged. "Genes and other genomic inventions remain patentable," said Q. Todd

Dickenson, Commissioner of Patents and Trademarks. Dr. Neal Lane, director of the President's Office on Science and Technology Policy also stated that, "nothing in the statement supersedes these (patent) criteria."

Perhaps the confusion on the part of investors stemmed from the mistaken belief that a raw DNA sequence can be patented, when in fact it must be accompanied by information regarding its function in human health or another potential commercial application. Dr. Haseltine, CEO of Human Genome Science Inc. summed it up by saying, "Trying to patent a human gene (sequence) is like trying to patent a tree. You can patent a table you made from the tree but you cannot patent the tree itself." Existing patent law protects the added value that is layered on the raw DNA sequence pertaining to its function or use in a specific application. The joint US/UK statement reinforces this concept.

The statement contains nothing new in regards to how private genomics and biotech companies can protect their intellectual discoveries. However, its effects demonstrate the importance of the perception of the long-term growth potential of this sector in garnering strong investment. It also highlights the need for the general public and investment community to have a deeper understanding of the patent process, especially with respect to the biotechnology sector.

Case Study: Celera Genomics

Perkin-Elmer (PE) is a leading manufacturer of DNA sequencers. In 1998, Celera Genomics, now regarded as a major competitor to the Human Genome Project, was created as a strategic unit by PE to take advantage of the company's core capabilities in creating biological technologies. Celera utilizes a GeneTag or cDNA amplification process to create primer pairs that are then "binned" or amplified in 128 pair capillary lanes, allowing for rapid identification of candidate genes.

After a stock split two years after formation and a valuation in the stock market that hit a record high of $247 US per share in February, 2000 from a low of $7 in June, 1999, Celera lost more than 2/3 of its value in one month after the issuance of the Clinton-Blair joint statement. Despite the market jitters, Celera's business has an impressive and widening web of alliances and contracts with big pharma. The company employs an aggressive business model and has already filed over 6,500 patents from its sequencing data. In addition to the device expertise that its parent company provides, Celera has engaged in an alliance with Compaq computer for computing power. Celera's genomic database subscribers include some of the major pharmaceutical companies in the world:

- Amgen, Novartis, Pfizer, and Pharmacia & Upjohn have subscribed for five years of access to Celera's databases

- Gemini Holdings plc has entered into a collaboration to discover genes and genetic polymorphisms associated with common, chronic, age-related diseases
- RhoBio S.A. has signed a three-year agreement for expression studies to discover genes related to traits of importance in maize
- Rhone-Poulenc Rorer has signed a three-year discovery agreement to identify therapeutic targets for a variety of human diseases

The potential for Celera and its subscribers to "lock up" the genomics market has spurred controversy about the company's practices, and has necessitated a formal participation from the American and U.K. federal governments. The concern is that a genotype-based medical system will result in genetic discrimination and segmentation of the biopharmaceutical market, with a quasi-monopoly on gene patents and their ensuing products. In response to the Clinton-Blair statement, Celera has indicated that the company intends to make their database publicly available to scientists and academics, however, they do wish to receive protection from other companies selling the in-house database developed by Celera.

Case Study: Affymetrix

Affymetrix is the most established international biochip company, and is a case study in the creation of strategic alliances to establish brand equity and marketplace leadership. Its GeneChip system is becoming the platform of choice for collecting, analyzing and interpreting genetic information. Affymetrix is involved in many joint programs to develop drug products arising from gene sequencing and expression data. A partial list of the company's many partners and customers includes:

- American Home Products
- Astra
- Bristol-Myers Squibb
- Eli Lilly
- F. Hoffman-LaRoche Ltd.
- Genetics Institute
- GeneLogic
- Glaxo Wellcome
- Hoechst
- Merck
- Metabolex
- Millennium
- Novartis
- Pfizer
- Pioneer
- Rhone-Poulenc Rorer
- Sanofi
- Schering AG
- Tularik
- Warner-Lambert/Parker Davis

Affymetrix is now involved in three business segments: gene expression profiling, polymorphism analysis and disease management.

Case Study: The SNP Consortium

This $45 million initiative is funded by the Wellcome Trust, academic institutions and 10 pharmaceutical companies, listed below:

- Astra Zeneca PLC
- Bayer AG
- Bristol-Myers Squibb Company
- F. Hoffmann-La Roche
- Glaxo Wellcome PLC
- Hoechst Marion Roussel AG
- Novartis
- Pfizer Inc
- Searle
- SmithKline Beecham PLC

In November 1999, the SNP consortium released its first set of 2,300 SNP markers available to corporations and researchers. The goal of the consortium is to identify the 300,000 markers distributed throughout the human genome, and to map at least 150,000. By November 1999, approximately 15,000 markers were identified. The pharmacogenomic data is expected to accelerate the arrival of "personalized medicine."

Case Study: QLT Phototherapeutics

QLT PhotoTherapeutics Inc., located in Vancouver B.C. is an originator and global leader in the nascent field of photodynamic therapy, which involves using light-activated drugs to treat disease. The company's team of 250 has worked for almost two decades to bring this technology to bear on conditions that targeted cell destruction can benefit.

The company provides products for several medical areas, and has formed partnerships in each:

- QLT has a worldwide agreement with CIBA Vision Ophthalmics, the eye care unit of Novartis AG, for the development of photodynamic therapy products, including VisudyneTM, as a potential treatment for a variety of eye diseases

- In the area of oncology, QLT has formed strategic alliances for the marketing and distribution of PHOTOFRIN®; Sanofi Pharmaceuticals Inc. in the U.S. and Caribbean, Wyeth Lederle in Japan, and Ligand Pharmaceuticals in Canada

- For cardiac surgery and treatment of heart disease, QLT established a partnership with Arterial Vascular Engineering, a division of Medtronic, to develop a therapeutic system for the reduction of arterial restenosis utilizing local delivery of a photosensitizer during angioplasty

Recent focus for QLT includes promising research in the areas psoriasis and rheumatoid arthritis.

Julia G. Levy, Ph.D. is President and Chief Executive Officer of QLT PhotoTherapeutics Inc.

http://www.qltinc.com/

Case Study: GlycoDesign

GlycoDesign's focus is the use of carbohydrate processing inhibitors or CPIs, which are small molecular inhibitors of enzymes that are responsible for the synthesis of carbohydrate structures that are involved in disease. CPI's prevent the normal activity of carbohydrate structures, which include control of growth and mobility of cells, activation of the immune system, cell adhesion binding of hormones and growth factors, and so disrupt the normal disease presentation.

GlycoDesign has a proprietary technological platform wedded to their approach to increase the efficiency of the process. The company uses bioinfomatics, genomics, and animal disease models, and utilizes high throughput screening and combinatorial chemistry to identify enzyme targets from libraries of chemical and natural compounds.

GlycoDesign has a number of CPI programs underway, including GD0039 (cancer, chemoprotection, anti-metastatic), Core2 (inflammation), GlcNAc-TV (cancer).

Jeremy P. Carver, B.A. Ph.D. is the President and Chief Executive Officer of GlycoDesign Inc.

http://www.glycodesign.com

Case Study: BioChem Pharma

BioChem Pharma is an international company based out of Quebec that focuses on development and commercialization of products for the treatment of cancer and infectious diseases.

Key products include 3TC/Epivir, which is available in more than 100 countries and has become a cornerstone of HIV treatment, and Zeffix, an oral treatment for hepatitis B. Both drugs are being distributed worldwide through a partnership with Glaxo Wellcome.

Until recently, the company also contained a diagnostics division, but after an internal review decided to divest the division and focus on therapeutics and vaccines. In July 1999, the company sold its haematology operations, and in March 2000 sold the remaining diagnostics operations.

BioChem Pharma has numerous research collaborations with Canadian universities and hospitals, as well as with several small biotechnology companies including Apoptosis Technology, Microbiotix, and Scriptgen Pharmaceuticals. In addition to their partnership with Glaxo Wellcome, they have commercialization agreements with Astra Zeneca and SmithKline Beecham for other products.

Francesco Bellini, Ph.D. is the Chief Executive Officer of BioChem Pharma Inc.

http://www.biochempharma.com

Chapter 3: Canadian Industry Overview

The following overview of Canada's biopharmaceutical industry has two parts. Part A provides general background on the industry and examines the industry value chain in detail. Part B provides the outcome of stakeholder consultations. As part of the analysis, key findings regarding technological capabilities of Canadian companies are analyzed.

Part A: Industry Value Chain

3.1 Background

In Canada, the biopharmaceutical industry has grown rapidly. The results are already promising, with revenues second only to those of companies in the United States. In Canada, there are about 85 well established and about 100 early stage biopharmaceutical firms. Due to the need for distribution networks and scientific expertise, companies are clustered in major cities like Montreal, Toronto and Vancouver (Life Sciences Research Investments, *Canadian Biopharmaceutical Companies*, 2000).

Canada's share of biopharmaceutical sales (at less than 2% of 1998 worldwide sales) will increase given that the number of products approved for sale in 2000 has increased to 16 from 12 in 1999. 1999 sales reached $207 million, compared to 1989 sales of $15 million from four drugs (BIOTECanada, *Canadian Biotechnology '98: Success From Excellence*, 1999 and Life Sciences Research Investments *Canadian Biopharmaceutical Companies: Status of R&D and Clinical Trials*, 2000).

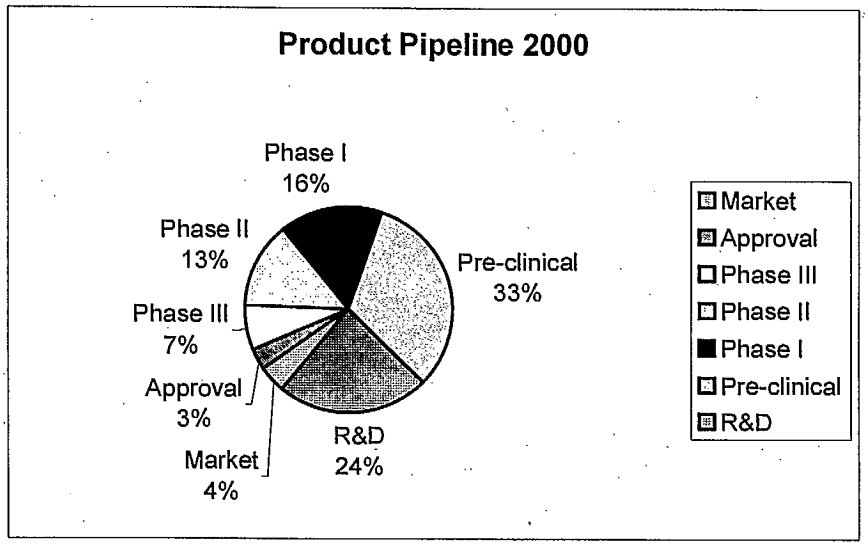
Three types of firms make up the biopharmaceutical industry structure in Canada:

1. Dedicated biotechnology companies developing pharmaceutical products
2. Research-based pharmaceutical companies
3. "Technology players" or specialized tier of biotechnology firms developing or relying upon technology platforms

Dedicated biopharmaceutical companies are usually organized around academic researchers who have developed a patented biotechnology product or concept in a therapeutic specialty. Technology players differ from dedicated biopharmaceuticals in that they sell or license their platform-driven products for royalties, rather than complete the last phase of clinical trial development. Pharmaceutical companies typically market the products that have been developed by biotech firms (Boston Consulting Group, *The Pharmaceutical Industry Into Its Second Century*, 1999).

Canadian biopharmaceutical companies are demonstrating their rapid rate of innovation with 372 products under development in 2000. The top four major therapeutic categories are cancer, central nervous system disorders and infectious and cardiovascular disease. Canadian companies are actively seeking opportunities to enter therapeutic markets that currently have unmet needs, e.g. cancer and AIDS (Life Sciences Research Investments, *Canadian Biopharmaceutical Companies*, 2000).

FIGURE 15: BIOPHARMACEUTICAL PRODUCT PIPELINE IN CANADA



Source: *Canadian Biopharmaceutical Companies*, Life Sciences Research Investments, 2000.

The Canadian biopharmaceutical industry is experiencing a rapid growth rate of 20% compared to the international growth rate of 10-15%. Future growth and competitive advantage will be sustained by innovation in basic research and by competition based upon product, rather than price.

3.2 Value Chain in Canada

Stage 1: Basic Research and Innovative Technology

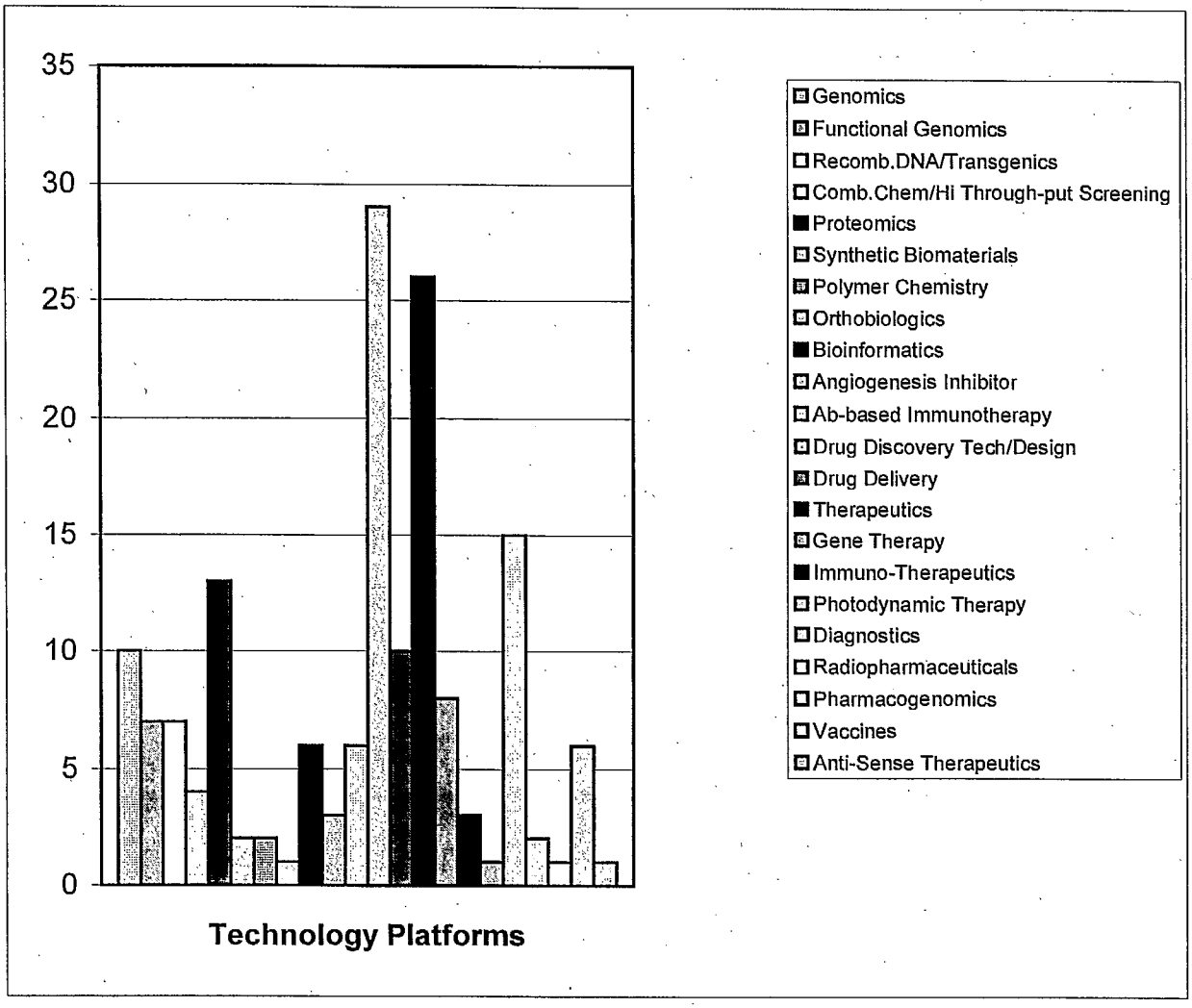
According to Statistics Canada, in 1998, companies with platform technologies such as genomics, bioinformatics and molecular modelling comprised 3% of all biotechnology companies. STRATEGIC HEALTH INNOVATIONS' overview of 146 biopharmaceutical companies indicates that more than 10% of sampled companies are now involved in genomics and bioinformatics. The rate of innovation in technology in the industry is clearly very rapid.

Such platform technologies, especially those related to genomics, have been the main focus of pharmaceutical strategies and alliances over the last several years. As well, genomics platforms have been the major research focus of academic institutions such as The Hospital for Sick Children and the Samuel Lunenfeld Research Institute in Toronto. Unsurprisingly, innovation in biotechnology platforms is the primary driver of the growth in Canada's biopharmaceutical industry.

Recognizing the potential to develop industry capabilities in genomics, Genome Canada—a newly funded government venture—is being created to support R&D in and commercialization of genomics technologies. Government granting programs are also important as a considerable number of MRC spin-offs are founded upon genomics technology (6 out of 30). These spin-offs are multiplying, are younger, have less foreign ownership and raise funds through the traditional route of capital markets (Medical Research Council, *Canadian Biomedical Spin-offs*, 1999).

Appendix 7 contains the data from an overview of the basic research and product development platforms of a sample of 146 biopharmaceutical companies in Canada. Data was collected using publicly available information. The information is summarized in the following figure.

FIGURE 16: TECHNOLOGY PLATFORMS UTILIZED BY BIOPHARMACEUTICAL COMPANIES



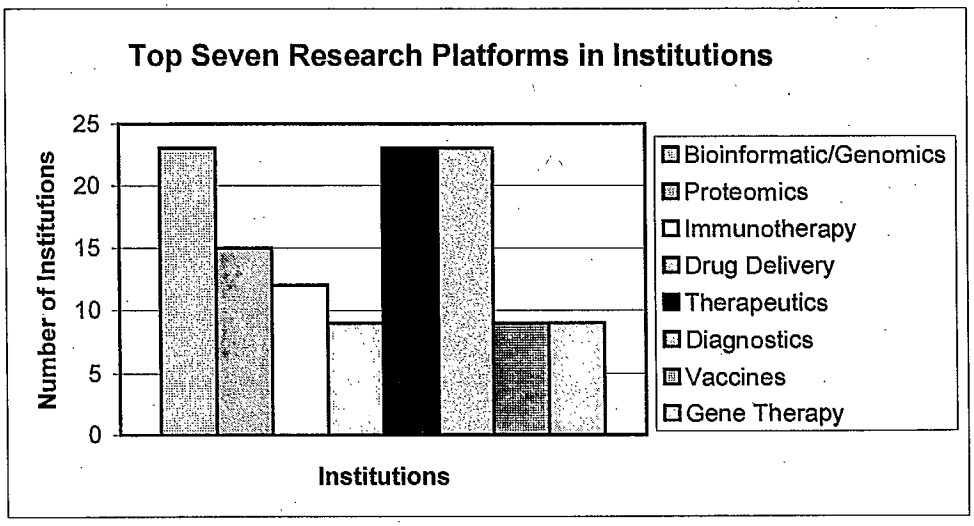
The top six technology platforms and specialty areas with the greatest industrial research concentration are:

1. Drug Discovery Design and Technology, i.e. general drug discovery platforms such as combinatorial chemistry and high throughput screening (19%)
2. Therapeutics, i.e. research in specific therapeutic areas (18%)
3. Diagnostics (10%)
4. Proteomics (9%)
5. Genomics and Drug Delivery Systems (7% each)

The analysis indicates that Canadian companies are concentrating on drug design applications, as well as platform technologies in genomics and proteomics. Many companies are also developing strong expertise in therapeutic areas. Lorus Therapeutics, profiled at the end of Chapter 3, is an example of a company that uses the "cluster" or "hub" strategy to gain critical mass in technologies directed at specific therapeutic areas. A significant number of biopharmaceutical companies are also involved in diagnostic R&D, integrating diagnostic test development with therapeutic product development. Another company profiled in a case study is Paladin Labs,

STRATEGIC HEALTH INNOVATIONS also identified the research capabilities of Canadian academic and medical institutions and networks. Thirty-three institutions were selected and their technological platforms were categorized. The goal of the analysis is to identify the innovative technologies arising from Canadian research institutions. Appendix 6 contains a summary of technological platforms in which research institutions are involved and a case study of the strength of the genomics platform in academic institutions is available at the end of Chapter 3. The case study demonstrates how Canadian research institutions and networks are leveraging their research strengths in genomics into commercial opportunities.

FIGURE 17: TOP SEVEN RESEARCH PLATFORMS IN ACADEMIC INSTITUTIONS



Canada's rich academic infrastructure provides most of the early stage research that drives new innovation. There are more than 60 academic and medical institutions in Canada that are involved in biomedical research. The focus on medical research is traditionally grouped by therapeutic specialty rather than by technology. In some cases, the technologies are receiving institutional priority in the form of a cross-departmental mandate, or targeted technological strategy, to further the institution's expertise and enhance its profile. In other institutions, there are single researchers using a particular technology platform in his or her research.

The top five research fields and technology platforms that are being developed in Canada are:

1. Genomics/bioinformatics
2. Therapeutic fields of research
3. Diagnostics
4. Proteomics
5. Immunotherapies

The University of Toronto is the academic institution with the broadest range and highest number (8) of technology platforms being developed, followed by the Clinical Research Institute of Montreal with 7 platforms. A number of institutions with 6 platforms are a close third, including McGill University, Dalhousie University, NRC Institute for Biological Sciences, NRC Biotechnology Institute and the Hospital for Sick Children.

Stage 2: Commercialization and Technology Transfer

In 2000, Canadian academic institutions are beginning to master technology transfer, with 30 MRC spin-off companies already reported.

Technology transfer offices and centres across Canada are major contributors to Canadian commercialization success in biopharmaceuticals. Two centres that are considered successes include Queen's University's Parteq and University of British Columbia's University-Industry Liaison Office (UILO). Parteq has issued 50 patents with 215 pending, while UILO has filed 800 patents in biomedical and engineering fields. UILO has spun off 90 companies while Parteq has almost 20 spin-offs. Twelve of UILO's spin-off companies are public and have a combined market capitalization of more than $8 billion. As of March 2000, Parteq has received more than $8 million in royalties. Over its history, Parteq has also negotiated more than 40 licenses and attracted $100 million in licensing funding (Queen's Gazette, March 2000 and Canadian Business, May 2000).

The creation of early-stage venture capital funds, such as University Medical Discoveries' Inc. (UMDI), Milestone Medica and T2C2, has helped Canadian companies gain access to the capital that was previously only available in the United States.

As well, the increasing support from institutions and all levels of governments for technology incubation has helped facilitate the transitive pathway from basic research to industrial success. Presently, there are three biotechnology industrial research parks in British Columbia, Saskatoon and Montreal. The government of Ontario has also recently announced a $20 million Biotechnology Commercialization Centre Fund to support biotechnology incubation in the province (NBAC, *Sixth Report*, 1998, www.strategis.ic.gc.ca and www.est.gov.on.ca).

Stage 3: Business Development, Access to Capital and Strategic Alliances

In Canada, strategic alliances with pharmaceutical firms are crucial for small biopharmaceutical concerns to secure the capital necessary for product development, regulatory approval, manufacturing and marketing. The most important reasons cited by Canadian biopharmaceutical companies for forming alliances are access to a sales force and sharing of resources to penetrate new markets (Price Waterhouse Coopers Lybrand, *High-Performing Strategic Alliances in the Pharmaceutical, Biotechnology and Medical Technology Sectors*, 1998).

Additional small investments by MNEs could continue the momentum that was created with the funding of the Astra Zeneca Research Centre in Montreal and Amgen Institute in Toronto. Notable new R&D investments in 1999 include Merck Frosst Canada's funding of a Chair in Cardiovascular Research at the University of Manitoba, Bristol-Myers Squibb's $18 million investment in the Cardiac R&D Centre, and Glaxo Wellcome Inc.'s creation of a Chair in Molecular Genetics at the Clinical Research Institute of Montreal. MNEs are also investing in manufacturing facilities in Canada, including AstraZeneca's $250 million facility in Mississauga and Pfizer's $10 million investment in its Arnprior facility (Rx&D, *Annual Review 1999-2000*, 1999).

Some of the key strategic alliances that have been formed by Canadian pharmaceutical companies are summarized in the table below:

TABLE 10: SAMPLE OF CANADIAN STRATEGIC ALLIANCES

Company	Partner
NPS Allelix Biopharmaceutical	Pharm-Eco Labs Eli Lilly Jansen Pharma
BioChem Pharma	Glaxo Wellcome Oncogene Science Beth-Israel Hospital, Harvard Warner-Lambert
Biomira	Chiron Biovector Therapeutics
Helix	PENCE/University of Alberta PharmaDerm Laboratories

Source: *Canadian Biopharmaceutical Companies*, 2000.

If even a small proportion of the drugs that are being developed in Canada are to be commercialized, the capital requirements are expected to be in excess of $1 billion, representing a significant investment in the biopharmaceutical industry over the next several years. Canada's venture capital infrastructure and support for biopharmaceutical research is also growing with new funds continuously created, including the Eastern Seed Technology Fund and the Canadian Medical Discoveries Fund.

Apart from the need for capital and expertise from strategic allies, the other pressing business development issue is skilled labour. Canadian companies find it difficult to attract technical expertise and internationally renowned scientists because of lower research funding, lower salaries and higher tax rates than found in the United States. Access to qualified managers who can oversee international biotechnology companies is also an issue as biopharmaceutical firms grow (NBAC, *Sixth Report*, 1998).

Stage 4: Product Development, Clinical Trials and Regulatory Process

In Canada, the requirements for regulatory approval of a drug are very similar to those of the FDA and Europe. In 1998, the turnaround time for drug approvals increased by 21 days to 570 days in 1998, however, it represents a significant decrease from the 1,163 days required in 1991 (Rx&D, *Annual Review 1999-2000*, 1999).

Drug efficacy and safety are monitored by Health Canada's Therapeutic Products Programme (TPP). There are significant changes underway that will improve the regulatory approval process for clinical trials and new drug approvals. The major changes are summarized below.

TABLE 11: REGULATORY APPROVAL MEASURES

HIV/AIDS WORKING GROUP ON THE DRUG REVIEW PROCESS	• Representatives from industry, HIV/AIDS community, researchers and government working to improve the approval process for drugs.
Cost Recovery – Phase IV	• TPP is in the last stage of evaluating cost recovery program in response to reductions in federal spending.
Investigational New Drug (IND) Policy Change	• Proposal to introduce a 48 hour registration period for Phase I (eliminating the existing 60 day trial period), and a 30 day default review period for all other phases (reduced from existing 60 days). Implementation is expected in September 2000.
Health Protection Act	• Modernization of the health protection system by replacing four existing statutes with the Health Protection Act.

Source: Rx&D, Annual Review 1999-2000, 1999.

Modernization of the drug approval regime will create value for biopharmaceutical companies and build up Canada's internationally recognized contract research industry that specializes in clinical trials. Other opportunities for clinical research organizations include the application of e-commerce to clinical trials, which will increase the processing speed of clinical trial data significantly.

Stage 5: Market Development, Manufacturing and Marketing Capabilities

Competitiveness in international trade is important for biopharmaceutical companies since their success is dependent upon the export of drug products to global markets. Policies that would enhance the position of Canadian biopharmaceutical firms include joint reviews of products by several countries and mutual recognition agreements that harmonize product approval globally. In 1998, mutual recognition agreements were signed with Switzerland and the European union in which Health Canada adopted guidelines for the international harmonization of pharmaceuticals (NBAC, *Sixth Report*, 1998).

Competitive drug pricing is an issue for both consumers and industrial organizations. A balance has to be reached between rising health care expenditures and the future viability of the

pharmaceutical industry. Canadian drug prices are currently 12% below the international median, and are expected to decrease in the future. The challenge is to curb health care costs but not at the expense of technological innovation in the industry (Rx&D, *Annual Review 1999-2000*, 1999).

Part B: Stakeholder Consultations

3.3 Stakeholder Consultations and the Value Chain

Background about Stakeholders

Stakeholders—both industry and academic—were asked about which stage of the value chain they considered themselves to be in 2000 and which stage(s) they plan to be in by 2005. About one-quarter of stakeholders consulted are involved in basic research and commercialization of that research and 17% conduct product development and clinical trials as part of their technological and company strategies. As companies move farther along the value chain, they generate higher returns on investment. It is therefore not surprising that most Canadian biopharma companies as well as some institutions have strategies for retaining their technological products in-house for as long as possible.

Successful companies and institutions incorporate innovative ideas in basic research, a well-defined vision, strong alliances and good management practices in their strategy. These organizations are developing novel technologies for the global marketplace. Their innovations attract attention from potential investors and partners, including large multinational pharmaceutical companies and Northern American venture capital funds. Companies and institutions that are proficient at business, product and market development also excel at creating the alliances needed to attain and maintain profitability.

However, at critical times in product development, biopharmaceutical companies may be forced to partner earlier than planned due to the high cash burn rate for R&D. Some companies have defined exit strategies for partnering with large pharmaceutical companies, or for out-licensing one product in order to feed the development of the other products in their portfolio. Generally, the trend is to retain control in-house for as long as possible. A case study of Theratechnologies, a company that is developing all stages of the value chain, is available at the end of Chapter 3. The case studies in this chapter are of companies and institutions whose representatives were consulted for the Technology Roadmap preliminary work report.

Approximately 17% of the stakeholders consulted identify themselves as being involved in all aspects of the value chain, ranging from basic research to marketing, while another 17% identify themselves as being involved in all stages except for marketing development. Academic institutions are involved primarily in the earlier stages of the value chain. The companies that are involved in marketing tend to produce information technology or diagnostic products. Presumably, these companies can market their products more easily because the costs of marketing and passing regulatory hurdles are much lower than those accrued for therapeutic products.

- **Key strategy for a Canadian biotech company is to retain products in-house for as long as possible.**
- **Early stage companies dominate the Canadian biotech sector**

TABLE 12. CHARACTERISTICS OF BIOPHARMA INDUSTRY IN CANADA

Characteristics of the Biopharma Industry in Canada	
Estimated Number of Companies	185
Number Consulted	36
No. of Major Academic Health Instns	>60
Number Consulted	6
Current stage in development	
Basic Research	10
Commercialization	3
Business Development	2
Product Development	6
From basic to product dev'pt	7
Market Development	2
Involved in all stages	7
Total	37

Stage 1: Basic Research and Innovative Technology

Approximately 60% of the participating stakeholders characterize themselves as being in the basic research stage of the value chain. Clearly, basic research in biotechnology is the engine that drives the biopharmaceutical industry in Canada. The challenge is to translate this strength into a diversified and successful product portfolio.

The consensus among participants is that Canada is globally recognized for innovation in basic research.

Analysis of Technology Drivers

As part of the consultations, participants were asked to identify the market drivers, i.e. the existing and future technologies that will contribute to the successes of the Canadian and international biopharmaceutical industry.

When asked to identify the most important Canadian and global technology drivers in 2000, 33% of the industry leaders stated genomics, followed by the general category of drug discovery technologies (10%), functional genomics (10%) and proteomics (7%). Regarding technology drivers for the next five years, the top response was functional genomics (29%), followed by proteomics (10%) and pharmacogenomics (10%).

TABLE 13. TECHNOLOGIES IDENTIFIED AS MARKET DRIVERS

Technologies Identified as Market Drivers

	Market Drivers			
	Current		Future	
Technology	**#1**	**#2**	**#1**	**#2**
Genomics	14		3	
Functional Genomics	5	3	13	7
Pharmacogenomics	2	2	5	2
Proteomics	3	6	4	3
Gene Therapy	1	1	3	1
Bioinformatics	3		3	4
Computational Chemistry				2
Nanotechnology			3	
Antibody-based	1		1	1
Tissue Repair	1	2	1	2
Microbiology (in drug synthesis)		2		
Combinatorial Chemistry	1			
Drug Discovery	3	3		1
Drug Metabolism	2	1		1
Drug Delivery		1		1
High Throughput Screening and Diagnostics	1		3	2
Herbal/Natural Drug Discovery			1	
Food/Agricultural			1	

Definition of Top 7 Technology Drivers

The top seven technology drivers are defined by STRATEGIC HEALTH INNOVATIONS and by participants. Some are discussed in greater depth elsewhere in this document.

1. **GENOMICS** is defined as a technological platform that utilizes analytic technologies, such as sequencing, positional cloning and functional genomic micro-arrays, to understand and characterize the human genome.

2. **FUNCTIONAL GENOMICS** is an extension of sequencing and a precursor to proteomics. Functional genomics is rooted in gene expression data collected from monitoring of the presence and abundance of different mRNA species in different cell types, tissues and disease states. Using DNA probe micro-arrays on glass chips, the level of gene expression at the genomic level is analyzed.

3. **PROTEOMICS**, the study of protein pathways that link genes to disease, is the next step in elucidating the human disease profile.

4. **DRUG DISCOVERY PROCESS** was defined by participants as the process of utilizing technological platforms to discover lead drug targets. The process can include screening of combinatorial chemical libraries, bioinformatics, high-throughput screening or a combination of any of these and other platforms to generate lead targets.

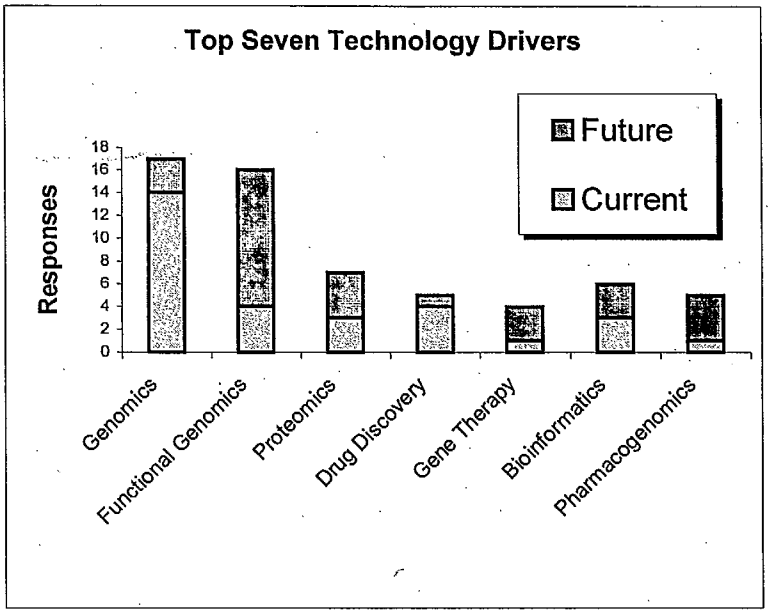
5. **GENE THERAPY** is the introduction of genetic material (DNA or RNA) into cells expressing a genetic defect.

6. **BIOINFORMATICS** is the use of software tools for data capture, analysis, mining and dissemination.

7. **PHARMACOGENOMICS** is the prediction of drug participation based on genotype.

The distribution of these technologies in terms of future vs. current importance is shown in the following figure.

FIGURE 18: TOP CURRENT AND FUTURE TECHNOLOGY DRIVERS



There was general agreement among the participants that Canada had an early opportunity to lead the world in genomics. Some of the first international genetic discoveries were made in this country, and the technological infrastructure to host a significant proportion of the Human Genome Project was present early on.

Now, Canadian companies are looking forward to the "post-genomics" era in which the information gathered from the Human Genome Project will be interpreted and applied to drug targets.

According to participants, this post-genomics era will include an increased emphasis on proteomics, functional genomics and drug discovery systems.

With the elucidation of the complete human genome nearing completion, the focus has already turned to understanding the protein products and functions of the gene. In the immediate term (1 to 3 years), functional genomics has been identified as a key driver in developing drug products and many companies are developing capabilities or products that are involved in interpreting genomic data. For the short term (3 to 5 years), participants believed that proteomics and drug discovery processes are important to the industry.

With the post-genomics era underway, the biopharmaceutical industry has renewed interest in the platform of proteomics. Using micro-arrays and mass spectrometry, collection of information about protein interactions is the next logical step in the evolution of the molecular biological drug discovery process. While many companies are engaged in genomics, functional genomics, and drug discovery, only one of the participating stakeholders consulted is focusing on proteomics.

The general consensus is that Canadians have the technological expertise to develop products that will drive the biopharmaceutical industry over the next 5 to 10 years.

Profiles of research institutions and companies involved in innovative research in genomics, functional genomics and diagnostics are available at the end of Chapter 3. The institutions include the Toronto Hospital, the Hospital for Sick Children and the Samuel Lunenfeld Research Institute. Companies include the bioinformatics company, BioTools, and Immucon, a diagnostics company that develops innovative contraceptive therapies.

Market Needs

Stakeholders were consulted regarding their perceptions of the met and unmet market needs for *technology*. During the discussions 68% of participants responded to this question and the answers mainly focused on unmet market needs which are summarized in the following table.

TABLE 14: UNMET MARKET NEEDS

Unmet Market Needs and Demands for Technology in Canada and the rest of the World

Top Stakeholder Responses

Improved drug technologies (enhanced properties of existing compounds, i.e. more efficacious, safe and easily administered)
Drug delivery
Lifestyle products
Herbal-based remedies and pharmaceuticals

Other Responses

Animal vaccines and animal and human immunopharmaceuticals
Nanotechnology
Food quality mechanisms
Technology independent user-friendly software
"Personalized" drugs
Models of protein activity (e.g. transgenic models)
Male infertility and male contraception
Novel methods of combinatorial chemistry
Products for the central nervous system
Pharmaceuticals for disease prevention
Global availability of sufficient and nutritious food supply

In contrast to the above market needs that are *not* being met by existing technologies in Canada, the following are some examples of market needs that Canadian companies are currently satisfying well:

- Cancer therapies, including anti-angiogenesis, chemotherapies and antisense therapies
- Biomaterials (bone regeneration), tissue repair and regeneration
- Products that address common diseases such as cardiovascular conditions will continue to be of primary importance

Technology Strengths, Weaknesses, Opportunities and Threats

Stakeholders were asked to identify the technological strengths and weaknesses, and opportunities and threats for the biopharmaceutical sector. Most comments regarding

technological weaknesses in Canada centred *not* around the scientific research but around the business environment for commercializing and developing technologies.

While there was almost unanimous agreement that Canada's major strengths reside in technological innovation, there were comments by 20% of participants regarding some potential technological gaps. The comments were varied and there was a lack of consensus on specific areas of technological weaknesses in the industry, primarily because Canadian executives and researchers viewed Canada's technology as the number one strength of the industry.

TABLE 15: CANADIAN TECHNOLOGY WEAKNESSES

In 2000 and 2005, what do you identify as Canadian technology weaknesses?
Companies are not information technology savvy
Lack of critical mass in bioinformatics, fermentation, high throughput screening, microbiology, and production of small molecules
Lack of synergistic effects to galvanize technologies
Lack of cross-sector collaboration (e.g. bioinfomatics requires IT, biotech, and statistics)
Lack of adequate facilities for animal studies
Outmoded academic system (institutional grouping based on therapeutic area vs. an institute that develops critical mass built on technologies)
Many companies stuck in phase between commercialization and product development

Stakeholders discussed Canadian technological strengths in general terms. There was wide acknowledgment that Canadians excel in all areas of research and a perception that Canadian scientific innovation can often exceed that of U.S. counterparts. There was also consensus on the fact that the business environment in Canada—comprising many factors such as smaller economies of scale, market and capital pool—lags behind the U.S. and increases competition for Canadian companies.

Approximately 79% of participants indicated in general terms that basic research is Canada's number one strength and a quarter of participants made specific comments regarding technological strengths and opportunities summarized in the following table.

TABLE 16: CANADIAN TECHNOLOGY STRENGTHS AND OPPORTUNITIES

In 2000 and 2005, what do you identify as Canadian technology strengths and opportunities?

Strengths

Basic research
Clinical trial infrastructure
Centres of excellence (e.g. Bacterial Diseases Network)
Research in medicinal chemistry and vaccines
Health care (and hospital) and social support systems
NRC
Drug delivery
CRO industry
Strengths in technologies including mouse models, proteomics, bioinformatics, gene hunting, founder populations in Quebec, Nfld, Hutterites, molecular biology and natural chemistry expertise
Presence of biotech incubators
Patenting process
High quality of raw stainless steel
Patient databases (ex. CF, Cancer Care, Quebec, etc)

Opportunities

Finding/creating niches
Tele-medicine and tele-health
To lead in areas where knowledge and expertise are important, e.g. structural biology, functional genomics and genetic epidemiology
To develop quantitative biology
To develop analytical technologies
To develop technology platforms in Canada where the platforms have not been established
To create both technology and service centres
To formalize patient databases
To develop stage of the art clinical trial expertise
To leverage the convergence of technologies

The comments were varied and, apart from emphasizing general basic research strengths, there was a lack of consensus on specific issues of technological strengths and opportunities. There was, however, consensus about the business opportunities for Canadian companies (see Chapter 4).

Themes in Basic Research
From the consultations, there emerged some common perspectives on Canada's ability to innovate in basic research:

1. **CANADA HAS A WEALTH OF SCIENTIFIC AND TECHNOLOGICAL EXPERTISE** that is waiting to be accessed and recognized.

2. **THERE IS A LACK OF CRITICAL MASS**, especially compared with the United States, in the promising technologies of the future.

For example, Canadians have been responsible for many international "firsts," including coining the term "functional genomics," developing capillary synthesis technology, and cloning the genes for Alzheimer's disease and cystic fibrosis. However, due to industry infrastructure barriers such as a lack of recognition of the value of Canadian technologies, Canadian companies have not been able to develop the critical mass needed for establishing an internationally competitive expertise in specific technologies. Challenges exist in first accessing and then retaining and growing this expertise within Canada in order to develop an innovative domestic biopharmaceutical industry.

Other common themes that emerged were the convergence of technology and the diversity of technologies now being developed.

Convergence of technologies is evident by the fact that most participants are collaborating across sectors with experts in information technology, physics, chemistry, mathematics, statistics and other fields outside their molecular biology specialties.

The convergence of technology is creating a barrier to research because there is a paucity of individuals with cross-sector expertise, e.g. a physicist who can also understand molecular biology, an information technologist who can develop a gene chip or an epidemiologist who understands genetics. The traditional academic disciplines are also being challenged. For example, several participants believe the traditional divisions between academic departments of biochemistry, pharmacology and biology need to be deconstructed because of the need for fluidity in the transfer of knowledge.

There is also recognition that the Canadian biopharmaceutical industry has to emerge from its traditional roots in academic therapeutic specialties and become more diverse in its product development. Companies that were started to treat diseases such as cancer must develop products for other market opportunities.

One-third of the industry leaders consulted emphasized that Canada must identify specific niches within the biotechnology industry to survive.

In essence, one or several niches must be identified within the industry to receive government or other capital support. During several consultations, Bombardier of Canada was given as an example of a Canadian company that developed a product to fit within a specific niche of the aeronautical engineering industry. This was suggested as a model for the future of the biopharmaceutical industry in Canada—one that ensures industry focus and strong government support. Some of the niches identified by the participants were proteomics, bioinformatics and microbiology in drug synthesis.

Stage 2: Commercialization and Technology Transfer

Institutions are becoming more proficient in commercializing academic research. Some participants indicated that the Network Centres for Excellence (NCE) are an important part of the commercialization process, and expressed interest in developing more intimate relationships with them. The three networks most often mentioned were:

1. Canadian Genetic Diseases Network
2. Protein Engineering Network
3. Canadian Bacterial Diseases Network.

It is also highly likely that the newly announced Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC) will be an important NCE initiative for the biopharmaceutical industry (http://www.nce.gc.ca/). The NCEs are considered to be a good concept with room for expansion, although some participants indicated that they could be more responsive to either collaboration or technology transfer suggestions.

While many participants applauded the increasing amount of spending for basic research that will probably be translated into commercial technologies and products, there was also frustration expressed about the uncertain infrastructure for further business development. Technology transfer was rated by participants as the six most important weakness in the biopharmaceutical industry. The amount of government spending on basic research was cited as being less than adequate for international competitiveness. Spending on basic research is viewed as the most important factor in driving the technologies and industry forward, however, the amount of spending in Canada was viewed by stakeholders as insufficient, especially compared to the United States.

Stage 3: Business Development, Access to Capital and Strategic Alliances

Due to the length of time for product development, companies need regular cash infusions from sources such as venture capital, private investors, equity markets and strategic partners. Many executives and researchers indicated that access to seed capital has improved. However, several

VC risk

companies that are currently involved in later rounds of financing indicated that they believe that they would have to become U.S. based enterprises in order to grow.

It was expressed that there should be a greater number of independent venture capitalists in Canada who are willing to allocate more mezzanine round funds to those who have surpassed seed capital and phase 1 funding. Almost half of the biotechnology industry leaders feel that Canada ranks second after the United States in such funding availability, although many felt that this may soon change. Participants believe that European venture capitalists are better "risk takers" and some of those consulted suspect that countries such as Germany will soon play a greater role in the biotechnology industry. The industry leaders claimed that, although many venture capitalists may be more risk averse, Canada was in a good position to compete with the global market, particularly if greater incentives are introduced for biotechnology business development.

Although many Canadian companies cited the competitive advantage that U.S. and European companies retain in being capitalized at a rate several times higher than their Canadian counterparts, there were some contrasting respondents who believed that there is enough money for those with the know-how to obtain it, and that lack of funds forces companies to be creative and innovative. Despite the oft-cited lack of a beneficial business environment, Canadian biopharma companies have been successful because of factors such as domestic expertise in technology, and an ability to recognize market opportunities.

Participants made some recommendations for improving the business development infrastructure, including the following:

- **FORMING A GOVERNMENT GRANTING PROGRAM** for small companies, similar to the U.S. Small Business Innovation Research (SBIR) and Small Business Technology Transfer (SBTT) programs that provide capital to companies in key expansionary phases

- **TAX INCENTIVES** to lure investment and skilled people to Canada; the Quebec model was cited as having a positive impact on the provincial biotechnology industry

- **EDUCATIONAL PROGRAMS** to include business teaching in order to foster entrepreneurial spirit in Canada's scientists and to educate government, the public and investors about biotechnology

- **A FORUM TO BRING TOGETHER INDUSTRY** such as a national conference for biotechnology, pharmaceutical, academic and government representatives to encourage strategic alliances

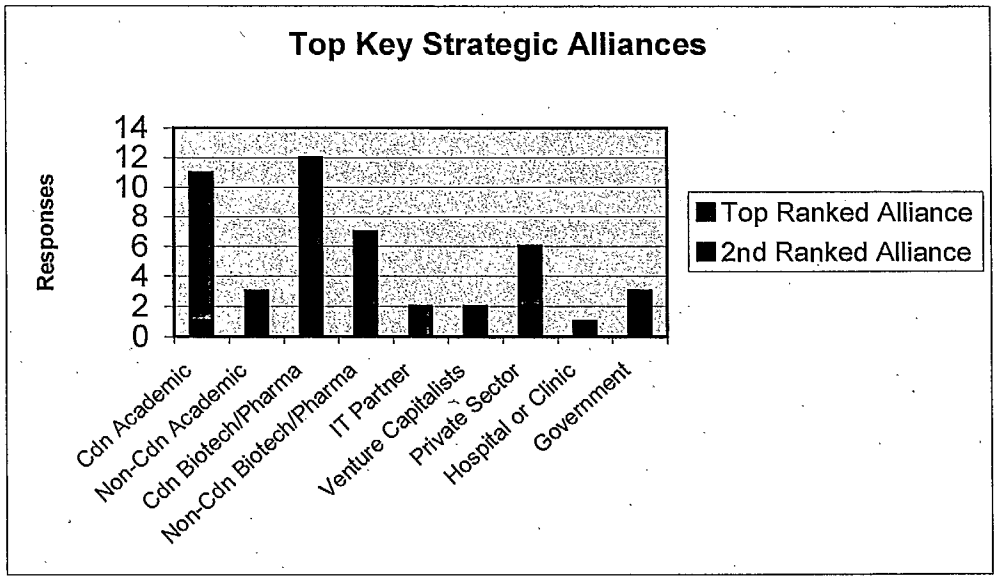
Participants were confident that the quality of science in Canada was comparable, if not superior to that of the U.S., but felt that, due to factors such as business infrastructure and lack of recognition of value, they might have to move to the U.S. in order to grow.

Key Strategic Alliances and Relationships

During the consultations, CEOs were asked to describe the key relationships and strategic alliances that will contribute to their technological success. Top responses included alliances with Canadian universities and academic institutions (24%) and both Canadian and international biotechnology and/or pharmaceutical companies (26%). Other top ranked alliances include general private sector relationships, government organizations and software companies.

The following figure summarizes the alliances that were identified by those consulted as advantageous to their company.

FIGURE 19: TOP RANKED STRATEGIC ALLIANCES



Paladin Labs and the Biotechnology Research Institute (BRI) of Canada are profiled in case studies of organizations with unique skills in forming key alliances. Paladin focuses on acquiring late-stage specialty pharmaceuticals through in-licensing while the BRI has had a number of commercial successes primarily because of its ability to attract partners.

Themes in Business Development

The limited number of domestic pharmaceutical companies, compared to the U.S., U.K. and Europe, and the strong pressure from U.S. competitors create a hypercompetitive environment for Canada's biopharmaceutical industry. The diversity of technology has increased so that pharmaceutical and larger biotechnology companies will have to rely on smaller, niche-oriented biotechnology ventures to provide them with the tools necessary for new drug discovery.

The result of convergence of technologies is that no one individual or company will have the expertise necessary to develop basic research and commercial products.

Ideally, every biopharmaceutical company will have a technical expert in areas such as physics, mathematics, statistics and information technology to complement the work performed by molecular biologists. At the moment, companies often rely on academic experts to do "piecemeal" research on specific projects and products. There is an opportunity to formalize the cross-sector academic and industry collaboration through vehicles such as the NCEs.

There was a perception among participants that there are geographic and provincial barriers to both networking and to exposure to potential strategic alliances. Some companies were also unaware of how to access funding programs at provincial or federal government levels. Increasingly, senior management is spending time on sourcing strategic alliances as the complexity of both the technology and the business environment increases.

A mechanism for creating linkages between the key stakeholders—government, academic, pharma, biotech, hospitals and NCEs—would enhance the business infrastructure for developing drug products in Canada.

Stages 4 and 5: Product and Market Development

Since most companies were not in the product and market development phase, these issues were raised as hypothetical ones for themselves and their strategic partners. The key issues related to product and market development that participants raised included:

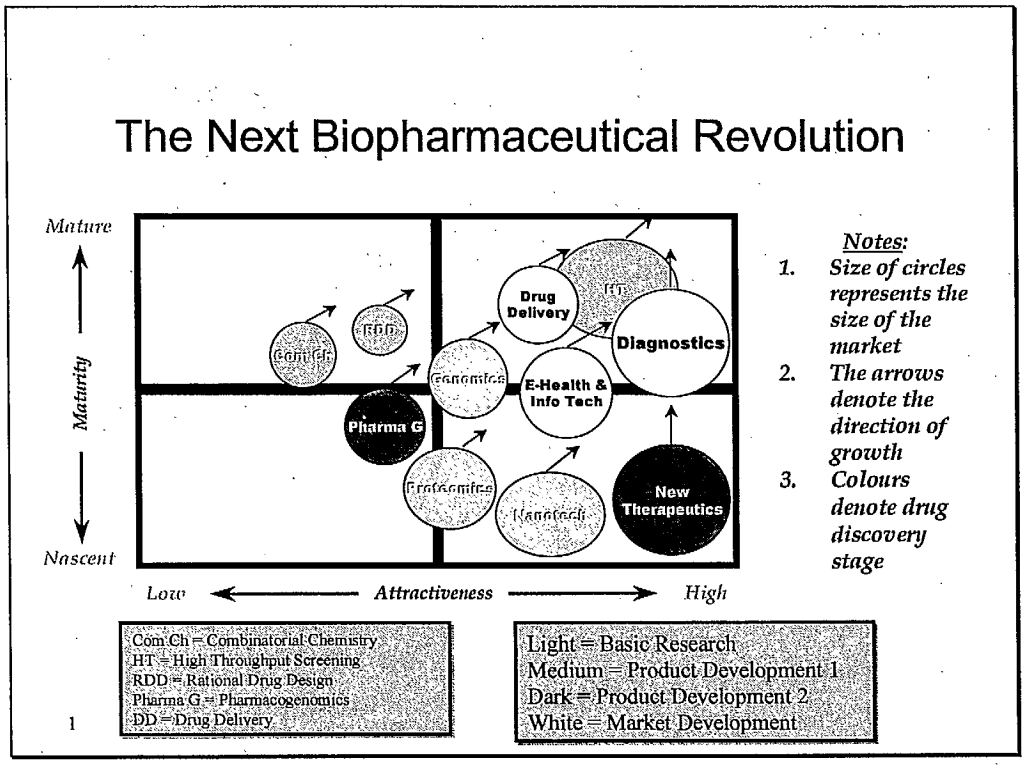
- **PRICING AND TRADE ISSUES** were viewed as potential barriers to foreign investment in Canada's biopharmaceutical industry
- **REGULATORY PROCESS ISSUES** were viewed as being improved but need to be benchmarked against leading jurisdictions such as the United States
- **NEED FOR INFRASTRUCTURE FOR CLINICAL TRIALS;** while it was believed that Canada has infrastructure for clinical trials superior to that of the United States, the common perception is that this infrastructure should be developed and taken advantage of.

There is an opportunity for Canada to lead the world in becoming the number one nation in clinical trials development. There is also a belief that clinical trials will become increasingly important in the value chain as the number of drug targets increases, resulting in increased competition for the pool of individuals available for clinical trials.

3.4 Summary Analysis of Key Technology Capabilities

Some basic trends emerge from STRATEGIC HEALTH INNOVATIONS' research analysis and stakeholder consultations.

FIGURE 20: TECHNOLOGY MATRIX



STRATEGIC HEALTH INNOVATIONS has classified the existing biopharmaceutical technologies according to level of technological maturity and market attractiveness. Some of the emerging technologies that will be highly attractive include nanotechnology, information-technology based platforms and new therapies, such as photodynamic and carbohydrate-based therapies. The mature technologies for which there is high market demand include gene chip technologies involved in high throughput screening and diagnostics and drug delivery systems.

In general, Canadian companies are largely small companies with therapeutic-driven basic research arising out of medical and academic institutions. The main focus of the basic research and product development is on developing technology platforms such as genomics, proteomics, and vaccine therapies. Recent developments in academic institutions include innovative and attractive technologies such as gene chips and nanotechnology.

Canadian companies also tend to be focused on the platforms associated with the early basic research stage of the value chain, rather than on later stage pharmacogenomics (SNPs) or supporting analytical technologies such as bioinformatics and high throughput screening.

Companies that do utilize broad-based screening tools often outsource them to centralized American centres, rather than develop them in-house.

Biopharmaceutical companies that integrate their technologies and systems across all aspects of the value chain or drug development process are in the minority in Canada. In the cross-functional technological areas, such as genomics and biochip development, broad capabilities are required in many platforms including information technology. Academic institutions in large urban centres that have critical mass in other industry sectors are starting to build these cross-functional capabilities.

In developing "toolkit" technology that focuses on equipment, Canadian companies may find it difficult to compete against international competitors that have economies of scale, scope and market penetration. In order to build scale, Canadian companies often form strategic alliances to help advance them in the drug discovery process.

Because of the enviable levels of technical expertise and infrastructure in Canada, there is an opportunity for investment in Canadian enterprises by international firms whose goal is to develop downstream drug products (e.g. rational drug design, transgenic models, pharmacogenomics and drug delivery technologies). Canada also has a highly developed industry of contract research organizations that can offer services that include expertise in clinical trials, information technology, and related research support.

Due to broad factors such as the early stage of the industry and the lack of local big pharmaceutical companies to partner with small companies, Canadian companies generally are not developing integrated systems for drug discovery, and are not focusing on later stage products and services—such as innovative drug delivery technologies or e-commerce health ventures—to create greater value.

While the Canadian health care system differs from that of the United States, and may not be as consumer-centred in the short term, Canadian biopharmaceutical companies must compete for the same international markets for their products. Innovation in biotechnology combined with value creation along the entire length of the value chain will help Canadian companies be global competitors, despite disadvantages of size and resource depth.

The quality of Canada's business environment is highly ranked (3rd out of 58 countries), and the cost of doing business within the Canadian pharmaceutical industry is significantly less than in countries such as the United States, Germany and France. This provides Canadian companies with a significant competitive advantage (KPMG, *The Competitive Alternative: A Comparison of Business Costs in Canada, Europe and the United States*, 1997).

Due to the early stage of evolution of the biopharmaceutical industry in Canada, there is very little emphasis among small companies on developing expertise in marketing development, or on moving downstream

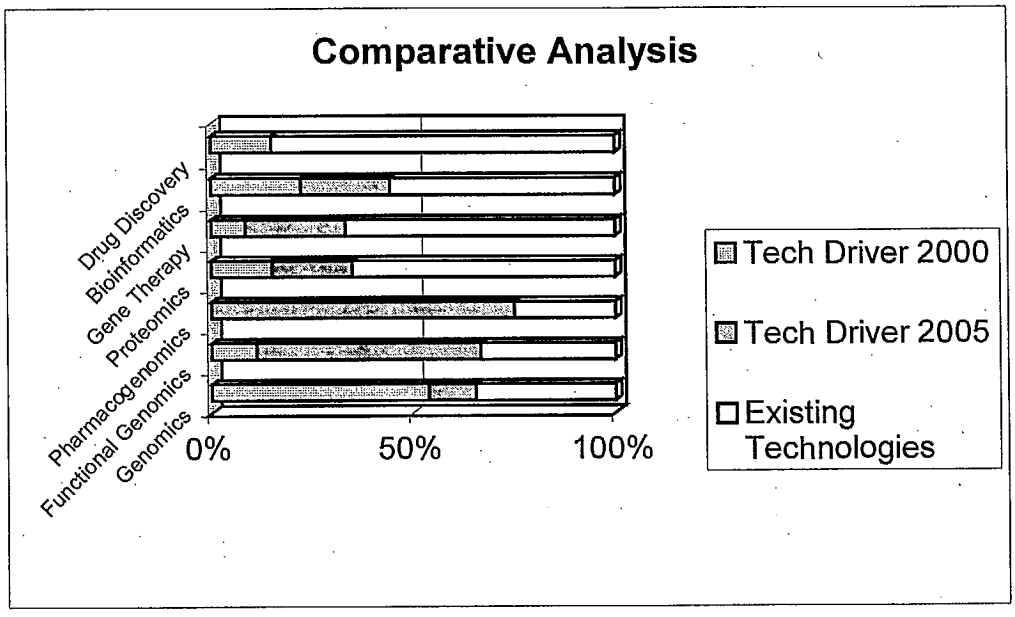
allying with other Canadian companies involved in activities in the later stages of the value chain. Canadian companies have the opportunity to increase the value of their products by ensuring that they move further down the development cycle and capture a higher return on investment.

While the focus on marketing development may differ in Canada compared to the U.S.—the largest market in the world for health care—due to a different model of health care, the underlying theme of decentralized medicine is the same. Hence there exists an opportunity for Canadian biopharmaceutical companies to develop expertise in health e-business, a hallmark of decentralization. This opportunity, of course, reinforces the stated need for a superior information technology infrastructure for biopharma interests.

Using the current business model of capturing more value as companies progress along the value chain, Canadian companies are engaging in activities across the entire value chain/drug discovery process—including marketing development—in order to be competitive with U.S. companies, and to gain access to international markets. A weakness in marketing capabilities exists domestically because there is a lack of Canadian owned big pharmaceutical ventures that could help take the research of small companies through to market.

3.5 Comparative Analysis of Industry in 2000 and 2005

FIGURE 21: COMPARATIVE ANALYSIS IN 2000 AND 2005



Stakeholders identified the technology drivers in 2000 and 2005. STRATEGIC HEALTH INNOVATIONS identified the technology platforms for 146 biopharmaceutical and related firms and summarized them in the above figure. The figure illustrates the fact that many of the technologies that stakeholders are predicting will be future market drivers are not currently being developed in biopharmaceutical companies.

A comparative analysis by STRATEGIC HEALTH INNOVATIONS indicates that there are gaps in the Canadian industry with respect to technologies that are driving the industry forward. For example, pharmacogenomics was identified as the top driver in 2005, while only one out of the 146 firms investigated is actively involved in pharmacogenomics research. Similarly, functional genomics was identified as the second most important technology platform and only 6 out of 146 companies are currently involved in functional genomics. A profile of Replicor, the only company consulted that focuses specifically on functional genomics, is available at the end of this chapter.

While stakeholders believe that basic research in technology is Canada's greatest strength, there appears to be a gap between basic research and translation of that research into industrial R&D and product creation.

Case Studies

Case Study: Hospital for Sick Children

The Research Institute at the Hospital for Sick Children is a world-class scientific facility specializing in basic and clinical research leading to the improved understanding, prevention, treatment and care of children's diseases. The Research Institute is one of the world's largest hospital-based paediatric research centres and is affiliated with the University of Toronto.

With over 540 research projects underway, the Research Institute houses a full spectrum of research activity, integrating biomedical research with clinical practice from basic science to clinical application in areas such as biochemistry research, cell biology, and genetics. In the past five years, thirty-two major research discoveries have been made at the Research Institute with scientists winning more than 70 international prizes and awards.

The Hospital for Sick Children has the following internationally recognized programs:

- Bioinformatics
- Centre for Applied Genomics
- Cystic Fibrosis Mutation Database
- Chromosome 7 Database (Human Genome Project)

HSC has become the leading genomics Centre in Canada. The Research Institute is also developing competencies in leading-edge and future technologies – such as animal medical imaging, computational bioinformatics – in order to position itself as a national and international leader in biomedical innovation.

Functional Genomics

There is a belief that if Genome Canada focuses on functional genomics, or on the application of genomic technology to disease pathophysiology, then a tremendous opportunity could be created for Canadians to lead the market in this area. Replicor Inc. is profiled as a company that is solely focusing on functional genomics. Replicor is a good case study of the innovative technologies and effective commercialization process in Quebec's well-developed biotechnology industry.

Case Study: Replicor Inc.

Replicor Inc. is a Montreal-based biotechnology company created in 1999. Replicor's directive is functional genomics.

By taking information learned from the human genome, Replicor can develop technologies for the treatment and prevention of disease.

Replicor's current focus is to develop applications of platform technologies based on regulation of DNA replication. Replicor's co-founder and CEO, Dr. Jean-Marc Juteau, explained that his company is involved in basic research (75%) and business development/commercialization /alliances (25%) of these technologies. The basic research is carried out in laboratory space provided by McGill University. The alliance with McGill University is essential to the development of these new technologies.

Products:

Replicor is focused on developing technology from mammalian origins of DNA replication and their regulation. A patent has been awarded covering an antibody against the cruciform structure formed after replication initiation. Other patents for proprietary technologies from McGill have been filed. Replicor has three major programs:

1. Applying origin of replication consensus, a 36 base-pair piece of DNA designed to incorporate vectors for gene therapy.
2. Technologies for modulating the initiation of DNA replication with possible application to controlling unwanted tissue growth (e.g., cancer or inflammatory disorders) or increasing tissue proliferation (e.g., tissue and organ regeneration).
3. Screening and designing compounds active at the site of human mammalian replication. The company is currently seeking collaborations, particularly with companies producing recombinant proteins where Replicor's technologies can be used to enhance production.

Financial Results:
Replicor Inc. is a young company, launched last year with C$450,000 of venture capital backing from Montreal-based venture capitalists T2C2. Replicor exclusively licensed its technology platform from McGill University.

Source: http://www.t2c2capital.com/replicor.htm; March 9, 2000 Consultation Jean-Marc Juteau, CEO.

Other Innovative Technologies

In addition to Canadian companies that are focused on drug discovery and therapies, companies in related areas such as diagnostics are developing technologies that are being recognized worldwide.

Case Study: Immucon Inc.

Immucon is a biotechnology company founded in 1993 in Montreal. Immucon develops and commercializes products in the field of contraception and fertility. With its innovative technology and niche market, Immucon is set to dominate a corner of the global contraceptive and fertility markets.

Immucon possesses a technology that could revolutionize the market of contraceptive products in the 21st century. While many contraceptive products presently exist, none has proven to be an ideal solution. The contraceptive field is still widely characterized by its unmet needs.

The company's immunocontraceptive products are intended for the male contraceptive and sterilization markets. The technology may later be used in the development of female contraceptive products as well.

As well, Immucon has developed an innovative technology to diagnose male infertility. Each year there are 2 million new infertile couples, meaning that approximately 8.5% of all couples worldwide are infertile. While female clinical reproductive tests are very elaborate, the number of available male clinical reproductive tests remains limited even though it is now acknowledged that male infertility accounts for 50% of all couples' infertility. Immucon is doing research on a cure to treat male infertility. Immucon hopes to have this cure on the market 5 years from now. Immucon is a perfect example of a Canadian biotechnology company able to supply an innovative technological product to meet a specific need in the global market.

Products:
Immucon has patented its novel male contraceptive technology to be commercialized between year 2005 and year 2007. In its research, Immucon has demonstrated that it can use a fragment of protein P26h to neutralize the sperm's fertilizing capacity acquired at the level of the epididymus. This immunocontraceptive technology targets a crucial zona-pellucida sperm binding protein acquired following the spermatogenesis. According to Immucon, the market for a male reversible contraceptive vaccine with a 12-month efficacy period, is approximately $US 850 million annually.

Immucon also has a new male infertility diagnostic test recently introduced into the market. Immucon's P34H Sperm Fertilizing Ability Test is currently available at a unit cost of $US 350. This test is a direct application of research findings in which low concentrations of a specific sperm protein, P34H, were found to be directly related to male infertility. It is specific and can identify the cause of infertility for 20% of all infertile couples. This technology will reduce the

number of women who may needlessly undergo invasive fertility examinations. The test may be performed as one of the first steps during the evaluation and analysis of an infertile couple.

Immucon is developing a female contraceptive pill to be taken once a month. This pill should have an efficacy comparable to existing oral contraceptives and will lack many of the known side-effects of the existing progesterone and estrogen based methods.

Source: http://www.immucon.com; March 9, 2000 Consultation Alain Bossé, President

Strategic Alliances

Strategic alliances with the information technology sector are becoming increasingly more important as the convergence of technology makes it increasingly difficult to rely solely on the tools of traditional molecular biology to discover product leads.

Case Study: BioTools Inc.

BioTools Inc. (BTI) was incorporated in 1995, making it the first Canadian bioinformatics company. It was created by 4 University of Alberta professors with complementary expertise in the fields of computer science (Dr. Jonathan Schaeffer and Dr. Duane Szafron) and biotechnology (Dr. Brian Sykes and Dr. David Wishart). BTI now employs approximately 20 full-time and 20 part-time employees, and boasts 2 successful bioinformatics tools on the market. In addition they have a potentially blockbuster diagnostic product in the development pipeline. BTI is involved in all stages of the value chain with respect to the development, marketing and sales of their 2 available software entities, GeneTool™ and PepTool™. Notwithstanding this fact, BTI has successfully utilized strong strategic alliances to help achieve continued growth.

Products:
PepTool™ and GeneTool™ are robust and innovative protein and DNA sequence analysis software products. These products garnered the "Best New Molecular Biology Products of 1999" award from *Biotechnology Software & Internet Journal* in December 1999, and are available both through a direct sales organization and directly from the company.

Although BTI continues to enjoy healthy sales from the 2 previously mentioned software products, their contractual agreement with Varian, Inc. to develop a new diagnostic tool may yield even greater payoffs. The Magnetic Resonance Diagnostic (MRD) project involves the clinical application of nuclear magnetic resonance (NMR) spectroscopy and advanced computational tools such as pattern recognition, to the diagnosis and monitoring of disease and health. This application also has potential applications in drug and toxicity testing. Varian, a world leader in NMR science and technology, has developed a state-of-the-art NMR system for the project including specialized sampling apparatus as well as providing a 400MHZ NMR spectrometer valued at U.S.$300,000 to BioTools for the duration of the project. Considerable

aid has also been supplied by local physicians in the recruitment of subjects for testing of the MRD process. Gordon Stranks, President and CEO of BTI said it best when describing the importance of securing a strong strategic alliance with an established world leader in a complimentary technology, "For a small but rapidly growing company such as BTI, entering into a strategic partnership with a multinational such as Varian is a significant step towards us achieving our goals for the MRD Project."

Financial Results:
Private investors contributed start-up and early round funding for BTI. In 1998, a private investment group, Western New Ventures Capital Corporation, provided a significant round of funding. Also in 1998, Sawady Technology Company Incorporated entered into a non-exclusive license to promote, market and sell BTI's custom peptide synthesis services to customers in Asia. The partnership was estimated to be worth approximately $US 500,000 in synthesis revenues to BioTools Inc. The Alberta Heritage Foundation for Medical Research (AHFMR) and the National Research Council's Industrial Research Assistance Program (IRAP) have also provided support for Biotools' growth. BTI continues to be a privately owned company. Additional capital is now being sourced to aid in the late stage development and market delivery of their diagnostic enterprise.

BTI's successful growth and market position over the last 5 years demonstrates the importance of combining strong fundamental science and appropriate strategic alliances in the development of a biotech company.

Innovative Strategies

Paladin Labs and Lorus Therapeutics are examples of Canadian company that have innovative strategies for accessing global markets. Paladin Labs is taking advantage of an overlooked market opportunity in licensing late-stage pharmaceuticals in specialty niche markets. The opportunity exists for Canadian companies to find such niche areas and develop international competitiveness. Lorus is acquiring companies and their technological platforms in order to build critical mass in key therapeutic technologies.

Case Study: Paladin Labs Inc.

Paladin Labs Inc., headquartered in Montreal, is a Canadian developer, marketer and distributor of innovative pharmaceuticals currently offering products in urology, dermatology, rheumatology and other specialty markets.

Paladin Labs' mission is to acquire and in-license late-stage pharmaceuticals that meet the needs of Canadian specialist physicians. Paladin's aim is to broaden these product lines as well as venture into new therapeutic areas. Paladin Labs' interest lies in market development, providing newly developed biotechnology to the Canadian market.

Paladin Labs Inc. was founded in 1995. Paladin is a public company whose shares trade on the Toronto Stock Exchanges under the symbol PLB. Paladin is one of the most profitable publicly traded biopharmaceutical companies in Canada.

Products:
In the past year, Paladin has aggressively in-licensed or acquired the Canadian rights to several innovative products, doubling the size of its product portfolio. The company has established comprehensive product portfolios in urology, dermatology and palliative care. Recently, Paladin negotiated the development, commercialization and supply agreement for recombinant human relaxin (ConXn®) with Connetics Corporation (Nasdaq: CNCT). ConXn® is a potential therapy for the treatment of scleroderma and organ fibrosis. Paladin will continue to grow its business at a comparable pace, and seeks business development opportunities for specialty therapeutics from several partners.

Financial Results:
Paladin has $12 million in current assets with a net profit of 1.9 million in 1999. The company is majority owned by Pharmascience Inc., one of Canada's largest and fastest growing pharmaceuticals.

Source: http//www.paladin-labs.com; March 9, 2000 Consultation Jonathan R. Goodman, President

Case Study: Lorus Therapeutics

Lorus Therapeutics is a small public company based out of Woodbridge Ontario that specializes in the development and commercialization of pharmaceutical products and technologies for cancer management.

Research and development focus in the company consists of discovery through to early (phase II) trials. Currently, the company is focusing on three avenues: anti-sense oligonucleotides that interact with segments of mRNA responsible for the production of overproduced proteins in cancer cells; compounds that interact with key receptors responsible for the synthesis of proteins overexpressed in cancer cells; and compounds that induce an immune response by macrophage activation.

Their first immunotherapeutic product, Virulizin for melanoma treatment is nearing approval, and they have two other products in early phase trials.

Recently the company acquired GeneSense Technologies in order to expand their pipeline of potential cancer therapies, and to gain access to some of the leading Canadian researchers in the field; Dr. Jim Wright and Dr. Aiping Young.

Lorus is building a technological hub with a two-fold strategy:

1. Technological strategy to utilize complementary strengths to develop a combination of products and therapies, to take a different angle of attack on cancer diseases, to have a large product portfolio to diversify and decrease risk, and to attract technology from other biotech companies.
2. Corporate strategy driven by market forces to form critical mass in order to access long-term capital.

http://www.lorusthera.com/

Case Study: Biotechnology Research Institute of Canada

The Biotechnology Research Institute in Montreal is an example of how creative strategies within research institutes can help the earliest start-up stage companies gain a footing in commercialization and grow.

The Biotechnology Research Institute of Canada (BRI) is located in Montréal with laboratories, offices and bioprocess facilities covering over 18,000 m². BRI maintains advanced facilities to carry out collaborative research projects in molecular biology and biochemical engineering. BRI's focus is basic research to develop a variety of biotechnologies with future applications in the Canadian and global markets.

BRI performs cutting-edge industrial R&D with some of Canada's leading firms, including Biomira, ABI, NPS Allelix, BioChem Pharma, Ibex Technologies, BioMéga, Glaxo Wellcome, Merck Frosst, and Syntex. The Institute takes a multidisciplinary approach to projects, bringing a diversity of experts together and providing them with the advanced technology required to carry out the project.

Companies can work with BRI through creative arrangements such as:

- **Collaborative research agreements where risk and cost are shared**
- **Contract agreements for the use of BRI's expertise**
- **Licensing agreements for the production and commercialization of products or processes**

Mandate:

The National Research Council's Biotechnology Research Institute is focused on making a significant contribution to the wealth generating capability of Canada, and represents a source of expertise for both the Canadian industry and the scientific community. BRI has two main objectives: (1) maintain excellence in basic research and (2) achieve an economic impact in the industry. According to Dr. Michel J. Desrochers, BRI's Director General, BRI is an indicator of the state of the biotechnology industry in Canada since the Institute serves to foster research and to create jobs, although it is not an incubator. A variety of products, patents and spin-off companies originated from BRI.

The Institute has three main divisions (1) Pharmaceutical Biotechnology, (2) Environmental Biotechnology and (3) Bioprocesses. The research groups of the Biotechnology Research Institute include:

Pharmaceutical Biotechnology	Environmental Biotechnology	Bioprocess
Gene Therapy	Bisensor	Microbial Fermentation
Eukaryotic Genetics	Environmental Microbiology	Separation and Purification
Enzyme Engineering	Analytical Chemistry	Cell Culture
Macromolecular Structure	Environmental Engineering	Process Control
NMR	Environmental Genetics	Enzyme Technology
Protein Chemistry	Ecotoxicology	Applied microbiology
Biomolecular Interactions		
Mammalian Cells Genetics		
Cell surface recognition		

Financial Results:
The National Research Council of Canada made the initial investment in 1987 of more than $60 million to develop BRI. The Institute manages an annual operating budget of approximately $23 million and half of the 400 people working at the facility are guest workers from industry and universities. BRI concentrates its resources on collaborative projects with Canadian industry, particularly companies working in the pharmaceutical and resource sectors.

Source: http://www.bri.nrc.ca; March 10, 2000 Consultation Michel J. Desrochers, Director General

Companies Capturing Value

The following case studies highlight an industrial company that demonstrates how value is being captured as biopharmaceutical products are developed in Canada.

Biopharmaceutical Companies
Typically, these companies are seeking to partner with either pharmaceutical companies or larger biotechnology companies in order to access the resources needed for final product development (Phase III or IV trials) and marketing. There are a limited number of companies whose strategy involves participating in *all* stages of the value chain, including late phase production, marketing and manufacturing.

Case Study: Theratechnologies Inc.

Theratechnologies is a Canadian biotechnology company, headquartered in Montreal, that develops and intends to market innovative therapeutic products through strategic partnerships. Theratechnologies has targeted present therapies that can be improved upon and health care categories and diseases that currently have no effective treatment.

The company aims to participate in all stages of the value chain because it believes that it has a competitive portfolio of products with large market opportunities which will only produce a significant return on investment if all aspects of the value chain are pursued in-house. The strategy is to form partnerships as late in the value chain as possible in order to maximize returns.

Theratechnologies focuses its efforts and resources on therapeutic products that are likely to generate significant interest in the health care and biotechnology industries, where market potential is considerable and continues to grow.

Theratechnologies is a company determined to maintain ownership of its technology and to form alliances as late in the chain as possible. Dr. André de Villers, CEO of Theratechnologies, emphasized the importance of forming alliances, but believes that it is a disadvantage to be based in Canada. The company has observed how large multinational pharmaceutical companies promote their local biotechnology interests above the Canadian counterparts. In recent negotiations with Hewlett Packard, Theratechnologies stipulated that production remain in Canada – a position contrary to that of Hewlett Packard.

Theratechnologies is a relatively young company but it has already spun-off three companies: Andromed, a medical instrumentation and device company; Ecopia BioSciences, a company focused on the discovery of novel antibiotics through the study of bacterial genomes; and "Pepco", a company focusing on the development and synthesis of therapeutic peptides.

Theratechnologies was founded in October 1993 and is currently listed on the Toronto Stock Exchanges (TH).

Products:
Theratechnologies has 39 different patents. The Company focuses its efforts and resources on two lead products, the photodynamic treatment (PDT) of cancers affecting bone marrow and GRF (Growth Hormone-Releasing Factor) analogues. The Company also holds a rich scientific portfolio, including a Vpr technology, a cardioprotective agent Protectazem™, a platelet-derived growth factor cocktail, an anti-biofilm solution and a bioactive coating for dental and orthopaedic implants.

Financial Results:
Revenues for the third quarter in 1999 amounted to $793,000 compared to $427,000 for the same period in 1998 (an increase of 85.7%). This increase in revenues is due partly to the sales and contribution of the affiliated company, Andromed, and to interest income. Research and development expenditures, before tax credits and grants, reached $1,234,000 for the third quarter in 1999, compared to $963,000 for the corresponding period in 1998. General and administrative expenses for the quarter amounted to $699,000 compared to $640,000 for the third quarter of 1998. The company continues to reduce losses and has renewed funding from the Société générale de financement du Québec. The company currently has access to over $30 million.

Andromed:
Andromed is the result of a partnership between Theratechnologies and Société générale de financement du Québec, a provincial government organization promoting economic development projects. Andromed is a high-tech medical device company, offering significant technological expertise in highly sophisticated medical devices. A fully integrated company, Andromed focuses on the development, manufacturing and marketing of novel medical devices having a high technological value and which contribute towards improving the quality of health care while reducing the overall cost of medicine. The Company has developed Stethos®, an electronic stethoscope which is marketed worldwide by Agilent Technologies (Hewlett-Packard Company), and SEQUS.®, software for the evaluation of health care services.

Source: http://www.theratech.com; March 9, 2000 Consultation André de Villers, CEO

Genomics in Research Institutions

Genomics is the focus of an enormous amount of research effort in Canada and internationally. The vast majority of Canadian research institutes are involved in genomics work (see table).

Unsurprisingly, the greatest concentration of activity in genomics research is found in Vancouver, Toronto and Montreal. A good example of the depth of this research in a large well-funded centre is that pursued in Toronto's Hospital for Sick Children. Gene discovery and functional genomics are presently being employed in the areas of oncology, respiratory disease,

virology, inflammatory bowel disease, haematology, immunology, inborn errors of metabolism, neuroscience, bone and muscular disease and in cystic fibrosis.

Another good example is the University of Toronto's proposed Centre for Cellular & Biomolecular Research (CCBR). The Faculties of Medicine, Biomedical Engineering and Pharmacy played key roles in the development of this proposed $92 million centre. Twenty five million dollars of the budget is to be supplied by the CFI (Canada Foundation for Innovation), with the remainder to come from provincial, university and private sector sources. It will focus on the following five interrelated research programs: Proteomics & Bioinformatics, Protein Structure, Animal Models of Human Diseases, Cellular & Molecular Bioengineering and Functional Cellular Imaging. By uniting outstanding scientists from three faculties in a single location, the Centre will offer a unique contribution to the forthcoming biomedical revolution

In contrast to the University of Toronto, a number of centres may have only a small number of individuals participating in this type of research. For instance, fewer than ten specific ongoing research projects with gene cloning or gene expression as a major focus are listed in Dalhousie University's Medical Research Services Compendium Database.

ACADEMIC INSTITUTIONS UTILISING GENOMICS TECHNOLOGY BASE

Vancouver
University of British Columbia
Vancouver Hospital and Health Sciences Centre
Providence health Care, St. Paul's Hospital Site
Canadian Genetic Diseases Network
Centre for Molecular Medicine and Therapeutics

Edmonton
University of Alberta

Calgary
University of Calgary

Winnipeg
University of Manitoba

London
University of Western Ontario
Lawson Research Institute

Toronto

Hamilton
McMaster University

Ottawa
University of Ottawa
NRC Institute for Biological Sciences

Montreal
McGill University
Clinical Research Institute of Montreal (ICRM)

Quebec City
Universite de Laval
Centre Recherche de l'Universite Laval
Clinical Research Institute of Montreal (ICRM)

Halifax
Dalhousie University

University of Toronto
Samuel Lunenfeld Research Institute
The Hospital for Sick Children
University Health Network
Sunnybrook & Women's Health Sciences Centre

Source: STRATEGIC HEALTH INNOVATIONS, 2000

Snapshot: The Canadian Genetic Disease Network – "From Genes to Therapies"

The Canadian Genetic Disease Network (CGDN) is a unique R&D initiative aimed at increasing Canada's international competitiveness in scientific research, and a strong commitment to commercializing technologies. It consists of a nation-wide consortium of leading scientists in human genetics. Researchers work with industry partners to conduct leading-edge science in an "institution without walls." Core Technology Facilities include genotyping, DNA sequencing, bioinformatics training, DNA fish mapping, transcribed sequence detection, genome alteration in mice and C. elegans, in vivo DNA analysis, proteomics and immunoprobes.

The CGDN has been awarded core funding through 2005 from the federal Networks of Centres of Excellence Program (NCE) via the Medical Research Council of Canada (MRC). In addition, the CGDN has numerous industry partnerships with established biotechnology companies that provide valuable expertise and facilities to aid in the development of patentable discoveries.

Affiliation with industry has been central to CGDN's ability to create new commercial capacity and formal partnerships. Affymetrix has an academic access agreement with CGDN for preferential access to GeneChip technology and volume discount pricing. An agreement between Schering Canada Ltd. and the CGDN management team led to the largest university intellectual property agreement in Canadian history for the discovery of two genes involved in Alzheimer's disease. The CGDN is an equity partner in the spin-off company Apoptogen, based on research on a family of apoptosis genes. An equity stake is also held in the gene therapy company, Neurovir, a venture in which the CGDN played a major planning and launching role.

Research Institutions

Research institutes have a specific mandate to develop basic research and then commercialize the products through vehicles such as spin-off companies. Research institutes are often affiliated with medical institutions and have access to such broad expertise to bring a product to market. For example, the "bedside to bench to bedside" approach that Dr. Lap-Chee Tsui takes in his research can be carried out at Hospital for Sick Children because of the expertise in both basic and clinical research available in that particular institution. The approach involves identifying the "bedside" need of patients, translating those needs into basic research "bench" projects, and then validating the resulting scientific theory with additional clinical "bedside" research.

Case Study: Samuel Lunenfeld Research Institute

The Samuel Lunenfeld Research Institute of Mount Sinai Hospital (SLRI) is one of the world's leading biomedical research facilities. Led by scientist Dr. Alan Bernstein, the SLRI is characterized by a great number of peer-reviewed publications, prestigious awards and a complement of international trainees. Occupying over 100,000 square feet of laboratory space, the SLRI has an annual budget in excess of $25 million, most of which is derived from granting agencies and corporate sponsorships.

In 1997, the Joseph and Wolf Lebovic Centre for Molecular Medicine was established at the SLRI, representing a unique partnership between all levels of government and industry to further basic genetic research. The centre focuses on the application of molecular genetic techniques to human disease.

The SLRI has three primary areas of research: Molecular Biology and Cancer, Development & Fetal Health, and Epidemiology & Biostatistics. The goal of these interrelated programs is to understand the function of human genes and how these complex pathways lead to diseases such as cancer, asthma, diabetes, hypertension, premature labour and inflammatory bowel disease. Other areas of research include connective tissue disorders and proteomics & bioinformatics.

The SLRI's strategy is to build its competences through economies of scope, rather than scale. By focusing on a limited number of diseases across all areas of the value chain, SLRI is developing niche expertise and international credibility.

The SLRI's perspective is that basic academic research provides proof-of-concept, while spinning off companies can help to provide the scale necessary for product development and subsequent commercialization. SLRI has already established spin-off commercial opportunities, and is involved in all areas of the value chain with the exception of market development.

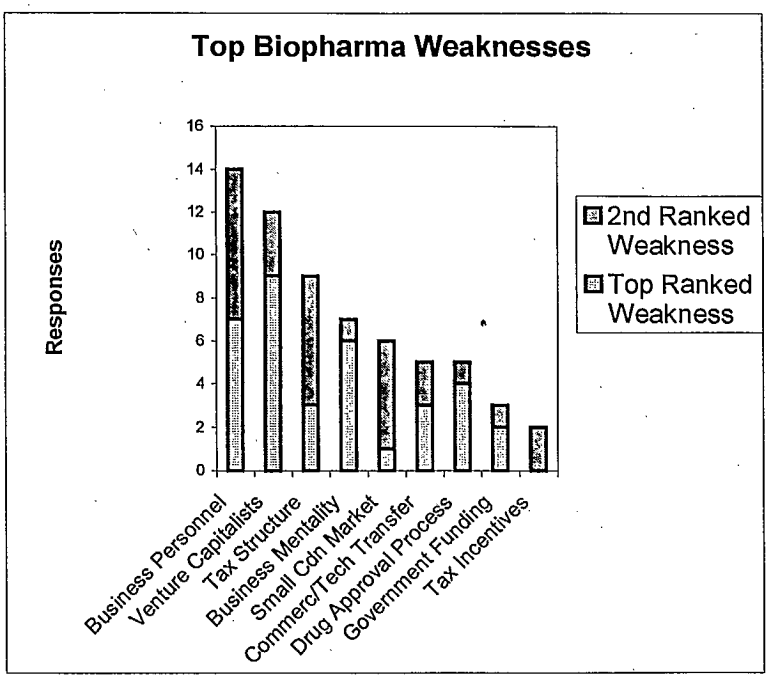
Chapter 4: Analysis of Consultations

4.1 Canadian Weaknesses and Threats

Weaknesses

The major perceived weaknesses of the domestic industry include the risk averse behaviour and limited funding of venture capitalists in Canada, especially in the intermediate phases (29%); lack of business skills in the scientific community (33%); and general "business mentality" in Canada (i.e. risk aversion) (17%). Some stakeholders also mentioned better identification of commercializable technologies. Notably, when asked to identify technological weaknesses, there were few responses to this question. Stakeholders overwhelmingly identified technological expertise as an important strength for the industry.

FIGURE 22: TOP BIOPHARMA WEAKNESSES



Perceived weaknesses are in infrastructure of business development rather than basic research and technology.

The six most important weaknesses (total responses ranked either as the number one or number two weakness) identified by participants are:

1. **LACK OF SKILLED HUMAN RESOURCES** in management and technical expertise.

2. **RISK-AVERSE VENTURE CAPITAL** in the domestic Canadian market. Many companies indicated that they are in financing negotiations with American venture capitalists. While there is a perception that U.S. venture capitalists are more aware of the value of Canadian technology, there is difficulty in accessing American sources of capital because of lack of access to the formal and informal relationships with the U.S. venture capital industry.

3. **TAX STRUCTURE** both federally and provincially, with the exception of Quebec.

4. **GENERAL BUSINESS MENTALITY** that perceives the risk but not the reward of biotechnology. There were concerns about the lack of entrepreneurial culture with the result that biotechnology is viewed as a risky industry with an environment that does not foster entrepreneurship. There was also a perception that there is a lack of understanding about the industry by federal and provincial governments and investors, including equity markets. Participants also cited bureaucratic barriers to business development. These include a lack of funding programs for Canadian companies in key expansionary phases.

5. **CANADA IS A SMALL MARKET** for drug products and Canadian companies need to compete with the U.S. market. There is a lack of large domestic pharmaceutical companies with whom Canadian biotech companies can form alliances. This acts as a barrier to further development of the industry. There is also a lack of Canadian expertise in performing national and international late phase product development and marketing

6. **COMMERCIALIZATION AND EFFECTIVE TECHNOLOGY TRANSFER.** An important barrier to basic research that stakeholders identified was the bureaucracy associated with the government funding process. There are an increasing number of government funding sources for basic research, each of which requires the completion of fund-specific timetables and conditions, creating a cumbersome application process.

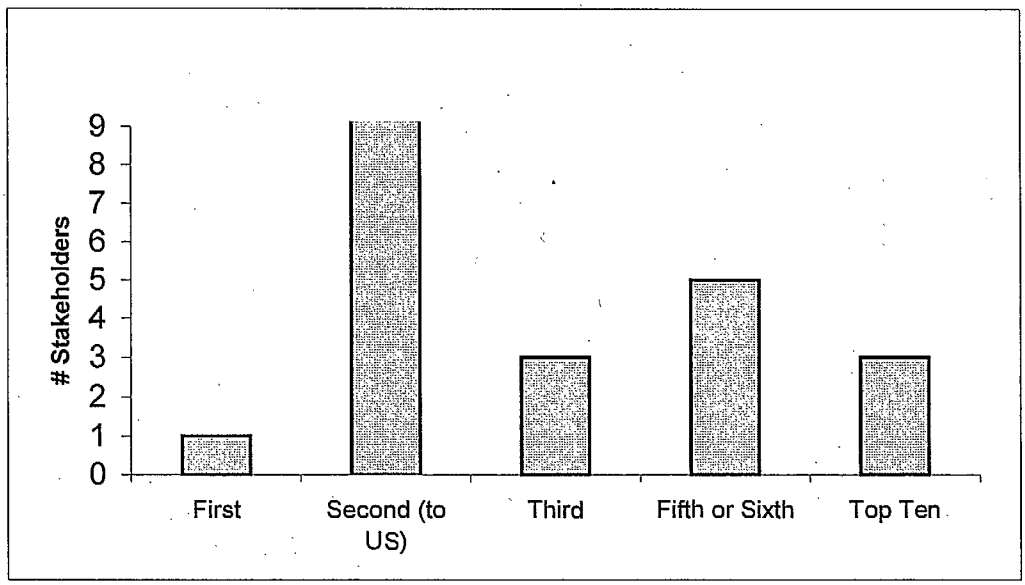
Threats

Some of the threats that Canadian companies face include:

- **INTERNATIONAL THREATS** from countries such as Germany and Ireland that have displaced Canada from 2nd or 3rd spot several years ago.
- **CANADA WILL EXPORT BASIC RESEARCH** and repurchase it at a more developed stage. There was a general concern that Canadian biotechnology will be sold to the U.S. at earlier stages than necessary, and that Canadian companies will therefore not realize the higher returns at later stages of the value chain. There was also a concern that Canada will export its skilled human resources along with the early products.
- **BEING RELEGATED TO "TOOLKIT" COMPANIES** that develop and then sell technologies, rather than develop health care drug products.
- **LOSS OF AN OPPORTUNITY TO DEVELOP A WORLD-CLASS REPUTATION** in a knowledge-based sector that will likely be one of the most important sectors in the global economy.

These threats were viewed as near or immediate-term. Participants indicated their belief that the timeframe for the Canadian industry to remain competitive could be as short as two years. Many pointed to the nation of Germany that, in the last year to 18 months, has taken significant measures in establishing itself as one of the top 3 countries excelling in biotechnology.

FIGURE 23: PERCEPTIONS OF CANADA'S GLOBAL COMPETITIVENESS



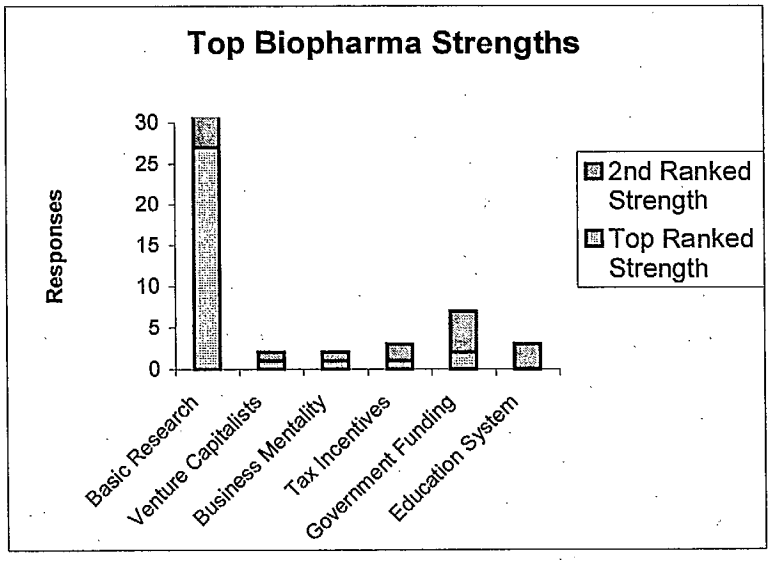
4.3 Canadian Strengths and Opportunities

Participants were also asked to share their opinion on the strengths and opportunities associated with being a Canadian biotechnology company.

Strengths

The majority of respondents (79%) specified basic research as the number one or two strength in Canada. The availability of government support was cited as an important strength by 17% of those consulted.

FIGURE 24: TOP BIOPHARMA STRENGTHS



Overwhelmingly, participants viewed basic research as Canada's top strength. A distant second was the availability of government support and funding.

1. **EXCELLENCE IN BASIC RESEARCH.** Stakeholders indicated that they believe that the technology expertise is prevalent but may not be well utilized and well integrated. While the rate of technology transfer within institutions has increased, there is still a belief that Canada has a wealth of expertise whose commercial value is just not being realized. One participant indicated that he believes that a mere 1% of all potential innovations are being commercialized.

2. **GOVERNMENT SUPPORT AND FUNDING.** The trend of increasing government funding support for companies was noted by several participants. Programs and agencies cited

include the Medical Research Council, Canadian Institute for Health Research, and the Technology Partnerships Canada program.

Participants also noted Canadian strengths such as: an excellent quality of life for employees, government support and funding for basic research, a strong educational system infrastructure and, in some provinces such as Quebec, well structured tax incentives.

Opportunities

Some of the key opportunities identified for Canada's biopharmaceutical industry are listed below. These are the areas that many participants believed could be capitalized upon to create international competitiveness.

- **POTENTIAL TO BE THE TOP-RANKED COUNTRY WORLDWIDE FOR CLINICAL TRIALS;** Canada has a heterogeneous demographic and a socialized medical structure that is ideal for conducting clinical trials. The formalization of clinical information across wide jurisdictions was viewed by more than half of the participants as an opportunity.

- **INNOVATIVE TECHNOLOGICAL NICHES** are specific market niches that are being overlooked either as a whole or in specific therapeutic areas. For example, drug delivery was cited as an important, stable and growing market and a relatively inexpensive method of innovating new drug products (e.g. $50 million compared to $300 million to develop). Other niches could include a targeted strategy to grow the portfolio for products targeted against a specific disease, e.g. cancer or heart disease.

- **LEAD IN AREAS WHERE CONVERGENCE IS IMPORTANT.** There is an opportunity to formalize cross-sector academic networking and develop leadership in cross-sector research such as bioinformatics.

- **LEAD IN AREAS WHERE KNOWLEDGE AND EXPERTISE ARE IMPORTANT** such as genetic epidemiology in founding populations or disease pathophysiology. There is a general perception that Canada cannot overtake the U.S. in building "better equipment" and that a way to compete was to further develop and capitalize upon the abundant scientific expertise in the nation.

4.4 Summary of Themes

The six most important themes that occurred in many consultations are highlighted below. It is important to note that while there was general consensus on these six themes, there were also some dissenting opinions.

1. **CANADIAN COMPANIES HAVE WORLD CLASS RESEARCH**, however, this value is not being recognized by investors.

2. **NEED FOR IMPROVEMENT IN BUSINESS INFRASTRUCTURE**—such as venture capital, a national industrial funding program and centralized funding for basic research—to capture the value from Canadian innovation

3. **CONVERGENCE OF TECHNOLOGY** is creating the need for cross-sector academic research and increasing the time spent on sourcing strategic partners.

4. **NEED TO IDENTIFY SPECIFIC NICHES IN WHICH CANADIANS CAN COMPETE**, such as clinical trials and innovative technologies, however providing business infrastructure to all companies will make Canadians more competitive.

5. **LACK OF CRITICAL MASS IN TECHNOLOGIES.** One of the most important themes that arose from discussion of the value chain was the lack of critical mass in technological areas in one region or province. While, on the whole, there is critical mass for specialties such as genomics across Canada, the geographical dispersion dilutes the cluster. Due to geographical dispersion and provincial barriers, there is a need for creation of infrastructure and community for industry to interact, learn from each other, collaborate and generate a Canada-wide critical mass.

6. **CANADA RANKS IN THE TOP 5 IN INTERNATIONAL COMPETITIVENESS** but that rank has fallen in the last 5 years.

4.5 Provincial Trends

While there was general agreement across Canada for certain themes, the degree of concern for issues such as business infrastructure varied from province to province.

Quebec

Quebec companies were the most satisfied with the business infrastructure, including R&D tax credits and tax holidays for employees that were made available to them by the province. McGill University was perceived to be an excellent academic support institution for its basic research and technology transfer expertise.

British Columbia

The NDP BC government was perceived as being "anti-intellectual" and without a mandate to focus on technology through tax incentives or government programs. For example, a provincial funding program for technology was recently reduced to $1 million from $12 million. There is also a perception that demographic provincial barriers (such as critical mass and venture capital)

make it more difficult for BC companies to form alliances with Eastern Canadian companies than with U.S. companies.

The incubator model for UBC's campus is highly regarded, and the biotechnology co-op program believed to be an important step in creating the management resources needed by the industry.

Ontario

The lack of tax incentives was a key concern for Ontario companies that are attempting to retain Canadian staff or to attract highly skilled workers from the U.S. Quebec was often pointed out as a model for the Ontario provincial government to emulate. The establishment of a fund for creating biotechnology incubators across Ontario was viewed positively.

Chapter 5: Recommendations

100% of consulted individuals expressed interest in participating in a Technology Roadmap Initiative. However, several concerns were raised including necessary time commitment, follow-through on results, and the format of the roadmap discussions. Generally, most respondents preferred a small, roundtable format that would feature representation from Industry Canada, e.g. the Deputy Minister and Minister of Industry, the venture capital sector, and government funding agencies, in addition to a broad spectrum of industry participation.

All those consulted indicated that they would be interested in participating in a Technology Roadmap Initiative.

5.1 Technology Roadmap

The recommendations that follow arise from specific discussions with participants about the Technology Roadmap Initiative.

1. Implement the Technology Roadmap Initiative for the Canadian Biopharmaceutical Industry. The participation from participants was 100% in favour of the initiative. However, participants did raise concerns about the project as outlined below.

   Action Step: Ensure that participants' concerns are addressed before and during implementation of the Technology Roadmap Initiative.

2. Examine models for different formats for implementing the Technology Roadmap Initiative. Participants indicated that small round-table formats with fewer than 15 people would be most productive.

   Action Step: Examine models such as the Ontario Jobs and Investment Board format of small round-tables in separate pools with final presentations to the entire stakeholder group.

3. Expand the Technology Roadmap to include other industry sectors and technologies that are important for biopharmaceuticals such as information technology, mathematics and physics.

Action Step: Pursue consultations with biopharmaceutical industry representatives in order to identify the other industries and their representatives that should be included from other industry sectors.

4. Ensure that the Technology Roadmap process is well designed.

   Action Step: Design Roadmap efficiently and effectively to ensure that individuals have a defined role as catalysts and that interactions between biopharma firms and companies from other industries are achieved.

5. Ensure that there is sufficient representation from larger biotechnology companies that can mentor/liaise with smaller ones.

   Action Step: Appoint a stakeholder from a large biotechnology/pharmaceutical company to access representatives from other large organizations.

6. Create an opportunity for follow through.

   Action Step: Ensure involvement of Deputy Minister and Minister so that industry retains confidence in the process.

5.2 Business Environment

These recommendations arise from the comments that individuals had regarding the business environment for the Canadian biopharmaceutical industry.

1. Increase the education to consumers, analysts and investors about Canadian biopharmaceutical opportunities in order to recognize the value in the market and implement training programs in the new critical fields of biotechnology.

   Action Step: Link together industry, BIOTECanada, the Biotechnology Human Resource Council of Canada and other organizations involved in educating Canadians about biotechnology.

2. Examine alternative models to existing business environment. Some models could include creating technology-specific or therapeutic-specific hubs, concentrating funding on fewer companies with niche and competitive concepts, and creating national tax incentives for industry.

Action Step: Examine models including Quebec's industrial tax incentives and Ventures West's new $200 M Technology Investment Fund.

3. Implement regulatory planning with foresight to approve future technological products such as pharmacogenomic products.

   Action Step: Liaise with Health Canada's Therapeutic Products Programme to formulate strategies for approving future technological products.

4. Celebrate successes in biopharmaceuticals in order to demonstrate responsiveness and excellence in industry.

   Action Step: Implement programs that identify key Canadian innovators in biopharmaceutical development.

5. Benchmark other countries with regards to business infrastructure for biopharmaceuticals. Some of the potential case studies cited by participants include the U.S. Small Business Granting Program and stock option taxation, Germany/Europe's potential to leapfrog Canada, and Ireland's government focus on decreasing taxes and improving investment opportunities.

   Action Step: Perform international benchmarking studies focusing on the U.S. and Europe.

6. Create a community or system for linking geographically disparate companies in order to obtain critical mass in technological expertise and knowledge transfer regarding business structure, e.g. availability of provincial and federal government funding programs and incentives.

   Action Step: Develop a national conference aimed at increasing strategic alliances and investment in the biopharmaceutical industry.

7. Ensure accurate and speedy dissemination of information regarding the availability of new funding programs and incentives.

   Action Step: Examine models for information dissemination.

8. Implement training programs in new critical fields of biopharmaceutical technologies.

   Action Step: Link with BIOTECanada and BHRC to develop training programs.

9. Interact with existing programs to highlight the new critical technologies.

   Action Step: Analyze the focus of existing government programs, such as Genome Canada and national and provincial funding programs, such as Technology Partnerships Canada.