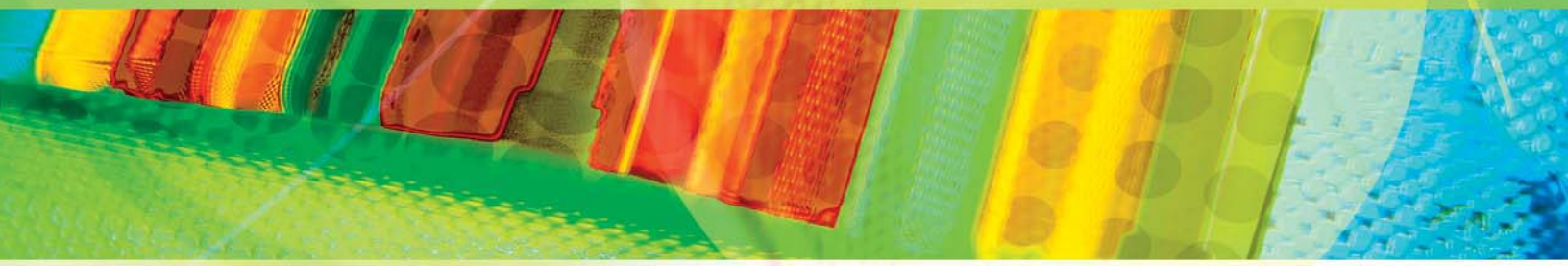
The Canadian Biopharmaceutical Industry Technology Roadmap

Challenges and Innovative Solutions



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A Technology Roadmap (TRM) is a tool used by countries to frame strategic decisions on where to invest public and private resources in technology-related industries. Its purpose is to assess the situation and plan for the future of the technology by outlining strategic choices for the most effective use of resources. It is intended to provide guidance to industry, government and the research and development communities. This TRM sets out an overview of the technological and scientific issues in the biopharmaceutical areas of greatest promise for Canada and then examines the new issues of commercialization. These issues have arisen as Canadian companies themselves undergo a transformation in response to the rapid evolution of technology and capital markets.

As Canada enters the 21st century, strategic investments in biopharmaceuticals will be increasingly important in improving the health and quality of life for Canadians, maintaining national prosperity and even dealing with issues of national security. The next five to 10 years will be critical for the maturation of Canada's potential in this industry and its pivotal role in clinical medicine, especially in the areas of genomics, proteomics, regenerative medicine, nanobiotechnology and novel plant molecular manufacturing.

The Government of Canada has identified biopharmaceuticals (by far the most significant component of biotechnology) as an important leader in innovation. Through increased investment in both public- and private-sector R&D, key strategic alliances, progressive regulatory and investment policies, increased student enrolment and management training programs, Canada will realize the economic potential of a home-grown and -developed biopharmaceutical industry.

Federal investment in initiatives such as the Canada Foundation for Innovation, the Canada Research Chairs Program and Genome Canada has put significant building blocks in place. The continuing partnerships among the federal government, agencies such as the Canadian Institutes of Health Research and the National Research Council (including the Industrial Research Assistance Program) and Canadian industry will be an integral part of positioning Canada as a world leader in biopharmaceutical discovery and technology commercialization. It is essential, however, that science, capital and commercialization be in place at the critical mass and coordinated levels required to ensure an entrenched and prosperous industry for years to come.

This document is designed to serve as a basis for continuing dialogue within the business, scientific and policy-making communities and externally with other important stakeholders, in order to provide guidance for future programs. It highlights the necessity for governments in Canada to rethink and readjust their support measures for this sector, so as to encourage it to prosper from new developments and to further the progress in our areas of scientific and economic leadership.

Dr. Anthony Schincariol,
Chair

Michel Noiseux,
Co-Chair

SYNOPSIS of the Champion of the Biopharmaceutical Technology Roadmap

Anthony Schincariol, PhD, MBA
President, Schincariol & Associates

Dr. Schincariol has held several positions over the last 25 years in the biotechnology and pharmaceutical industry. This included: President & CEO, Viventia Biotech; President & CEO, Novopharm Biotech; Senior V.P, Corporate Development, DUSA Pharmaceuticals; General Manager, Synergen Canada; Director, Prof. & New Product Development/Marketing & Scientific Director, Genentech Canada; and Director, New Product Development & Medical Administrator, Boehringer Ingelheim Pharma. He has had responsibility for new company start-up. R&D, business development, regulatory, intellectual property and marketing for several biological products including tPA, human growth hormone, gamma interferon, pulmozyme, interleukin-1 receptor antagonist and levulan. He has also consulted to several biotechnology companies on product development. Dr Schincariol also served as marketing Assistant in the New Business/ Technology Program in the School of Business Administration, University of Western Ontario. Prior to completing his MBA he was on the faculty of the University of Western Ontario with appointments in the Cancer Research Unit and the Department of Biochemistry. He received his doctorate from the University of Toronto, Department of Medical Biophysics in the Ontario Cancer Research Institute. Postdoctoral studies were conducted in the Department of Microbiology & Immunology, Duke University. He also served as a reviewer on grant panels for the Medical Research Council and the National Cancer Institute of Canada.

Reading the Roadmap

The TRM is divided into two parts. The first, the Science Challenges section, examines current issues in biopharmaceutical research and drug discovery, the convergence with nanotechnology, and biomanufacturing. A segment that benchmarks Canadian research, discovery and patents against its international peers is also included here. The Science section concludes with recommendations for strengthening Canadian biopharmaceutical science performance. The second part, Commercialization Challenges, deals comprehensively with Canada's biopharmaceutical commercialization challenge. It discusses opportunities, outlines the industry drivers and development requirements, reviews industry structures, and then looks at issues of financing and technology transfer at the start-up and development stages of company progress. The extensive and wide-ranging discussion offers a detailed portrait of the commercialization challenge and concludes that the current national approach needs to be refocused to nurture strong companies. Changing that strategy is essential if the industry is to grow in Canada. The commercialization section then concludes with a detailed matrix of recommendations and a proposed action program.

Methodology and Acknowledgements

The Biopharmaceutical Technology Roadmap process was championed by Dr. Anthony Schincariol, piloted by a Steering Committee, and facilitated by the Life Sciences Branch, Industry Canada. These pages comprise an overview of some of the major barriers in the biopharmaceutical development process, of preclinical and clinical development, of current research initiatives and of advances needed to overcome these gaps. The data and recommendations were compiled from a set of workshops, panel discussions, and interviews among stakeholders from industry, academia and the government. Further input was gathered from a CEO Forum charged with identifying solutions to barriers and from published literature.

The Steering Committee piloted the project and assimilated advice from industry experts emanating from the business, scientific and policy communities and supported by the men and women of the Life Sciences Branch, Industry Canada, under the direction of Dr. George Michaliszyn. The final report was developed by Dr. Anthony Schincariol and Mr. Michel Noiseux, President of Michel Noiseux, Bio-conseil, with assistance from Mr. Mario Perek, Life Sciences Branch, Industry Canada. Dr. Guy Stanley, Universities of Ottawa & McGill, served as chief editor. Dr. Kelly Butler was science advisor for numerous early drafts. Ms. Ingrid Pongratz, Life Sciences Branch, Industry Canada, served as project co-ordinator.

Research was provided by consultants from Science-Metrix (Montreal), Secor (Montreal), SHI (Toronto), James G. Heller Consulting Inc. (Toronto), and Dr. Paul Arnison, FAAR Biotechnology Group, Ottawa. The Roadmap team also acknowledges with thanks the assistance received from the Toronto Biotechnology Initiative, BioQuebec, BioteCanada, the Canadian Institute for Health Information, the National Research Council, and the Canadian Institutes of Health Research (CIHR).

Executive Summary

The underlying vision: a strong Canadian bioscience base with a mature, world-leading biopharmaceutical industry, working to advance knowledge and create wealth for Canada and Canadians.

— The Biopharmaceutical Technology Roadmap Steering Committee

Canada's biopharmaceutical industry is a world leader, particularly when our population and economic output are taken into account. Especially impressive is the number of biopharmaceutical companies Canadian scientific entrepreneurs have created. Based on the *'omics revolution*[1] — a science that is less than 10 years old — Canada's biopharmaceutical industry has created 490 companies and generates $3.8B in revenues.[2]

However, the industry is also growing explosively in the US, Europe and the Asia-Pacific region, and every nation is vying for investment. As global competition for investment capital intensifies, Canada must succeed not only in company formation but also in enabling new companies to grow in value.

Currently, too many Canadian biopharmaceutical companies lack the resources and capitalization to survive in this more difficult environment. This is in part because of the way Canada now funds early-stage commercialization. Without changes to Canada's current approach to innovation, it is by no means clear that sufficient numbers of Canadian companies will grow to their full potential. Under these conditions, the risk is that discoveries of Canadian bioscience will be sold off at fire sale prices, their full value reaped by more robust international competitors with greater financial strength. Without a strong Canadian biopharmaceutical industry, it would ultimately become more difficult to justify the resources currently devoted to the science base.

The report argues, however, that this outcome is far from inevitable. Instead, Canadian policy-makers must take concrete steps to ensure that when more Canadian biopharmaceutical start-ups go public they are strong enough to attract private capital on a competitive basis. This is not simply a question of finding more public money; rather, it is about the way that public money is spent, the incentives created by public programs and the ways to improve them to achieve the necessary goals.

The scientific inputs for continued and even enhanced Canadian success are clearly in place. Even though virtually every international analysis shows that compared with other leading countries

[1] One impact of genomics — the study of the human genome — on life sciences is to make every element of the cell into an 'omics specialty, such as proteomics for proteins and metabolomics for cellular fluids. Chapter Two contains a broader discussion of this point.

[2] Statistics Canada, Canadian Trends in Biotechnology, 2nd Edition (2005), Figure 12, p. 25.

Canada continues to under-fund its science base, Canadian bioscience is achieving impressive results. In terms of outstanding scientific publication, Canadian researchers continue to rank among the best in the world, especially in the areas of genomics, tissue regeneration and nanobiology. In addition, Canada has a very real potential to become a world leader in novel bioprocessing techniques. Our scientific successes in this area potentially form the basis for the next generation of commercialization platforms. The impact of the 'omics revolution in general, and of its application to the areas of Canadian excellence highlighted in the technical section of this report, are examples of what Canada can achieve to advance human health and in the process, revolutionize clinical practice.

Because of the urgent situation that the biopharmaceutical industry now faces in Canada, the main recommendations of this report focus on commercialization. The proposals are aimed at strengthening early-stage companies so that they can advance further along the development chain: from proof-of-principle to Phase I, II and III clinical trials and finally to full regulatory approval of their therapies.

That said, while we have our problems, Canada's biopharmaceutical sector should not be underestimated. It can perform. During the '90s Canadians grew companies of considerable value, although a number of them were ultimately acquired by larger global players. This report underlines the fact that Canada has the necessary elements to continue and even enhance its leadership in biopharmaceuticals. In particular, it has the scientific base and the entrepreneurial drive. The main problem afflicting commercialization is that companies are in too many ways over-encouraged to spin off from research and become dependent on private funding before they are fully ready to face the rigorous competition of today's private capital markets. This is discussed more extensively in the commercialization section of the report.

Once it is recognized that the root of Canada's commercialization problem is the premature birth of promising companies, contributors to this problem become evident at virtually every level of Canada's innovation system.

- Universities emphasize the numbers of start-ups they produce rather than their quality and strength.

- Governments award grants that emphasize scientific measures instead of business success measures. Some private investors maintain that there is sufficient capital in Canada for strong companies, but that there are too many start-ups with insufficient strength.

- Mid-stage companies also receive inadequate investment, leaving them with insufficient resources to complete clinical testing. Consequently, they resort to limiting product development to one or two products, a risky strategy that is often unsuccessful.

The recommendations below and the rationales set out in this report show how to overcome these problems and move forward. The underlying vision: a strong Canadian bioscience base with a mature, world-leading biopharmaceutical industry, working to advance knowledge and create wealth for Canada and Canadians.

Key Recommendations

Canada should re-examine its existing programs of support for R&D and early-stage commercialization with the aim of generating more robust companies, better able to attract investor capital. That means:

Research spin-off companies should be enabled to build up their management teams, intellectual property positions and proofs of concept before advancing to private markets.

An examination of funding available for early-stage companies transitioning from research settings to commercialization suggests that programs now in place need to be made more flexible and to be given more resources. Some jurisdictions — notably the US — have created special programs to accomplish this goal.[3] Canada might achieve similar results through such existing programs as Industrial Research Assistance Program (IRAP), Technology Partnerships Canada (TPC) (or its successor, if any) or CIHR's Proof of Principle program, if the enterprise-readying objective were to be made explicit and applications criteria appropriately adjusted.

University industry liaison offices should be encouraged to devote resources to readying companies for approaching capital markets.

In many cases, current emphasis is on rapid revenue generation from often premature technology licensing. More appropriate would be to encourage universities or third-party technology evaluation funds to act as investment banks, combining where necessary different small companies and their technology to make a more attractive and robust new enterprise.

Despite some positive changes in the immigration rules, a great deal needs to be done both in immigration and taxation if Canada is to succeed in attracting supremely capable international managers here to pilot Canadian companies.

Some provincial initiatives — in particular those of Quebec — show the kind of imagination and initiative required. But to be fully effective, such programs need to be generalized to the national level.

A complete set of commercialization recommendations with a proposed action program appears in Appendix 1, and a list of science recommendations appears in Section 1.7.

[3] One example is the Small Business Industrial Research (SBIR) program designed to enable early-stage companies in strategic sectors to advance to proof-of-principle stage in order to maximize their chances of successful commercialization.

Part 1
Scientific Challenges

1.1 Introduction

A burgeoning elderly population in industrial nations, underlined by longer life expectancy, will be the most important factor in the growing demand for drug therapies. The number of North Americans over the age of 65 is projected to double by 2030 to 70 million, which will put ever-increasing pressure on health care budgets. The inevitable result will be an increase in cancer, chronic diseases such as arthritis, diabetes and heart disease, and neurodegenerative disorders such as dementia, all of which are age-related.

Cancer, the second leading cause of death exceeded only by heart disease, is poorly served by traditional chemotherapies and a major opportunity area for drug development. The most notable research trend is the push to targeted therapies, which are tailored to patients who overexpress certain tumour receptors or are designed to interfere with specific signalling pathways. However, these therapies will require the development of companion diagnostic tests (theranostics) to determine which patients are most likely to respond to the therapy. More recently, "cocktails" of multiple targeted therapies are under investigation, as they may be more efficacious. In any event, virtually all cancer drugs face a significant hurdle in establishing efficacy in late-stage disease.

Stroke, the third leading cause of death, would benefit from faster diagnosis and therapies with a wider window of opportunity or, in the long run, from therapies that can encourage brain cells to repair themselves. Congestive heart failure is the most common reason for hospitalizations for people over 65; prognosis is poor and there is a need for drugs with a novel mechanism of action. Alzheimer's and Parkinson's diseases affect the quality of life of millions of people and are a major health care expense. Drugs that can better delay disease progression will be a big improvement over existing therapies. Other age-related illnesses such as osteoporosis, arthritis, diabetes, and liver and kidney diseases also offer significant areas for research breakthroughs.

Infectious diseases will remain a dominant feature of international public health policy for the 21st century, driven by increased global population, poverty, international travel, and sexual practices. Food production operations are a reservoir for new infectious agents such as SARS, bovine spongiform encephalopathy (BSE) and influenza H5N1. With the exception of research into HIV and more recently bioterrorism, the anti-infectives market has been neglected. Antibiotics have helped cure bacterial infections but there is a need for new classes with novel mechanisms of action that can combat the growth of drug-resistant strains. The development of antiviral drugs against viral infections, particularly respiratory, has proved to be much more difficult. Most therapies on the market or in clinical development are aimed at HIV, herpes viruses, and hepatitis B and C. However, resistance is likely to develop when the drugs are used for long periods to treat chronic conditions such as HIV, resulting in the need for novel classes of antivirals.

Serious infections for which no vaccines are available include *T. pallidum* (syphilis), *Chlamydia trachomatis, N. gonorrhoeae, E. coli* strains responsible for urinary tract infections, herpes simplex virus, respiratory syncytial virus, Group A streptococcus, *Chlamydia pneumoniae*, hepatitis C and E, and cytomegalovirus.

Research on active immunization has been extended to non-infectious agents, most notably cancer immunotherapy, as well as drug addiction, contraception, autoimmune disorders such as diabetes, and Alzheimer's. The development of the first vaccine that prevents cancer — against human papillomavirus related to cervical cancer — is a medical breakthrough. Vaccine development costs have increased substantially, however. It remains to be seen whether a differential pricing strategy can continue for newer products, in order to make them affordable in developing countries.

The discovery of recombinant DNA technology over 25 years ago was the impetus to the impressive progress in the application of biotechnology to the discovery, development, and manufacture of medicines and vaccines, a field broadly defined as biopharmaceuticals. The availability of complete genomic sequences for human and other organisms, combined with advances in molecular and structural biology, imaging methodologies, nanotechnology, and bioinformatics,[4] will have a significant impact on the way medicine is practised in the future.

Effects will range from more precise diagnostic techniques to more effective vaccines and patient-targeted therapies. Pharmacogenetics will help define the treatment population and drug dosages more accurately. There will be a redefinition of some diseases based on their underlying genetics and mechanisms of action. Targeted molecular therapies will prevail in treating cancer and other diseases. Advances in neuro-imaging and metabolic maps of the brain will enable neurosurgeons to treat cerebral ischemia and trauma. Cell transplantation will restore functions that are lost due to trauma-related cell death and neuro-degeneration.

However, many congenital developmental disorders and complex diseases such as hypertension, arthritis and autoimmune conditions involve more than one gene. Years of effort will be required to identify the relevant genes and proteins and how they interact. A similar challenge exists for conditions that have both a genetic and environmental component, such as obesity, asthma, atherosclerosis, certain mental illnesses and addictive disorders.

Over the next five to 10 years, we hope to see:

- rapid diagnosis of pathogens, new antivirals, and new and better vaccines;
- new classes of antibacterials effective in combating antibiotic resistance;
- cancer therapies for individual patients based on their genetic profiles;
- therapeutic cancer vaccines;
- methods to target specific therapies to specific sites including the brain; and
- reduction of $100M in drug clinical development costs by improving clinical success rates by 25% or reducing times by 20%.

Prospects over the next 10 to 20 years include:

- tissue regeneration as an alternative to transplants or synthetic implantable devices;
- survival rate improvement of 70% for most cancers;
- promotion of the functional recovery of the heart muscle;

[4] Computerized techniques for sorting, storing, analyzing, manipulating and mining biological information stored in databases.

- prevention of diabetes;
- development of vaccines for autoimmune disorders;
- treatments for challenging conditions such as stroke and degenerative diseases such as Parkinson's and Alzheimer's diseases; and
- treatments for addiction, including possibly vaccines.

Whether these predictions are realized will depend on many factors. Current industry productivity has declined in terms of new molecular entity development, and long-term safety is a key problem. Improving research and development (R&D) productivity through lower attrition rates, quicker termination decisions or faster development times would have a major impact on the cost and success of new drug development.

The cost of new drugs, particularly for chronic illnesses requiring lifetime treatment, will present a major challenge to the health care system. Effects will include a growing use of cost containment measures and demands for evidence that the therapies demonstrate substantially improved efficacy and cost-benefits such as decreased mortality, increased quality of life, functional improvement, shorter length of therapy, dosing frequency, or reduction in public health expenditures. However, this will be a challenge due to differences in the cost of health care inputs from country to country combined with the lack of standard study methodologies.

The Biopharmaceutical Technology Roadmap provides an overview of some of the critical knowledge gaps in drug discovery, clinical development, and biomanufacturing that underpin R&D productivity, costs and the rate of new product launches. Nanotechnology and tissue engineering will also be discussed, as these constitute major technology platforms that will impact the industry. The greatest near-term commercial impact of nanotechnology will be in new tools for basic research, followed closely by targeted drug delivery. Clinical applications such as diagnostic imaging and sensors, as well as scaffolds for cell and tissue engineering are longer-term goals. Many of these will not be realized for 10 years or more because significant research advances must be achieved and then validated by regulatory agencies.

The objectives of this review are to identify the advances needed to fill the knowledge gaps and to influence cooperation among industry, academia, and government, for progress in medical research requires the collaborative efforts of all parties. However, a detailed discussion of technologies and market demands in particular disease areas is beyond the scope of this report.

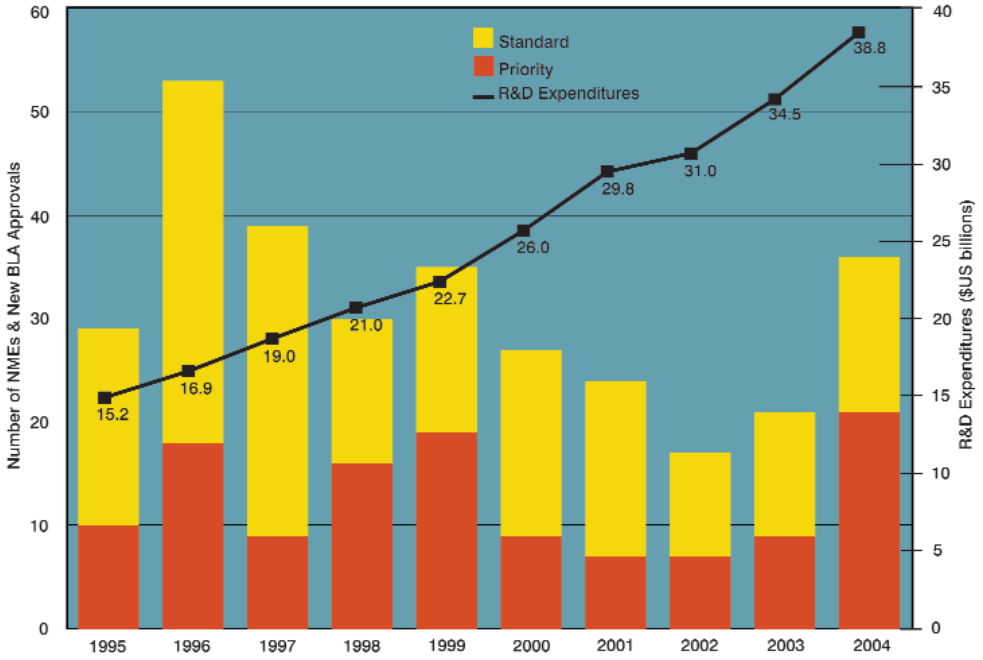
From 2002 to 2004, Canadian gross domestic expenditures on R&D in the health field averaged about 22.8% of all R&D, up from less than 18% prior to 2001. The largest performers were the higher education sector (universities and teaching hospitals) and business enterprises, which in 2004 accounted for 60% and 35% respectively of all health R&D. Strategic investments in R&D will not only improve the health and quality of life of Canadians but also have a strong economic impact on Canadian industry. However, a major challenge for Canada will be in capturing the industrial benefits of this research. Few Canadian biotech firms are vertically integrated, depending on multinationals for financial, marketing, and manufacturing capability, and there is insufficient capital to support clinical development through to Phase III trials and regulatory approval. Also needed is a strategy to better differentiate Canadian industry from its competitors in specific niches in order to attract investor attention.

1.2 Technologies to Improve R&D Productivity

1.2.1 Background

US industry R&D expenditures increased about 11% a year from 1995 to 2004 to US$38.8B, but the number of new molecular entities and biologics launched did not grow concomitantly (Figure 1). (The figure uses US data, as the US market serves as the industry benchmark.) The high cost of drug development contributes to risk aversion, because companies tend to focus their R&D efforts on larger markets and most promising candidates or drugs with an incremental advance over existing therapies.

Figure 1: US Pharmaceutical R&D Expenditures versus Approvals for New Molecular Entities and New Biologic Applications



Note: New molecular entities and new biologics contain active substances that have never before been approved in the US. Priority approvals represent significant improvements over marketed products while standard approvals have therapeutic qualities similar to those on the market.

Source: Pharmaceutical Research and Manufacturers of America; Food and Drug Administration Center for Drug Evaluation and Research, 2004 Report to the Nation.

Drug discovery[5] accounts for an estimated 25% of R&D costs (Table 1) and 45% of development time (Table 2). It has outgrown the overall growth rate of R&D expenditures over the last few years driven by the increased use of tools such as genomics, bioinformatics, combinatorial chemistry and high-throughput screening. These technologies have had minimal impact on R&D productivity when measured by the number of drugs that have entered clinical trials and moved to regulatory approval. Whereas a drug entering Phase I trials in 1985 had a 14% chance of reaching the market, success rates in 2000 were an estimated 8%.[6] For drugs that do make it to the market, 50% have suboptimal pharmacokinetic and

[5] Research to find connections between diseases, molecular targets such as an enzyme or receptor protein implicated in the disease process (biology phase), and drug molecules (chemistry phase) capable of modulating the biological activity of the target.

[6] Food and Drug Administration, Challenge and Opportunity on the Critical Path to New Medical Products (March 2004).

safety properties.[7] Also, only 22 drugs approved between 1994 and 2001 modulated newly discovered targets.[8]

Table 1: R&D Investment by Function (2001)

Stage	Percentage
Discovery	25
Preclinical	7
Phase I	7
Phase II	11
Phase III	23
Regulatory Approval	12
Phase IV (Post Marketing)	11
Uncategorized	4

Source: Pharmaceutical Research and Manufacturers of America, Annual Membership Survey, 2003.

The time for drug development excluding regulatory review is about 14 years, with the attrition of unpromising compounds occurring at every stage. A limited understanding of a gene's function or the biological pathways involved in the disease process is a major factor in the high attrition rate for many drug targets. The targets selected may be poorly linked to disease or the off-target effects may be greater than expected. Increased investment in new targets to develop first-in-class drugs will not necessarily solve the productivity gap, however. The Centre for Medicines Research International (CMR), a leading provider of pharmaceutical R&D performance indicators, recently reported that between 2000 and 2002 only 3% of projects based on new targets reached the preclinical stage compared with 17% based on known targets, and the former took 16 months longer on average.

Table 2: The R&D Timeline (in years)

Stages	Estimated Time
Biology	
• Target identification, prioritization	1.0
• Target validation	2.0
Chemistry	
• Combinatorial chemistry & screening	0.5
• Lead optimization	2.7
Development	
• Preclinical	1.6
• Clinical	6.0
Regulatory Review	1.5
Total	**15.3**

Source: Tufts Center for the Study of Drug Development, Boston Consulting Group.

[7] J. Hodgson, "ADMET—turning chemicals into drugs," Nature Biotechnology (August 2001), p. 722.
[8] Christopher Dobson, "Chemical Space and Biology," Nature (December 2004), p. 826.

Because target selection decisions drive all subsequent spending, a pressing need exists for better technologies that can reject unsuitable candidates as early as possible to improve overall success rates and reduce clinical development time frames and costs. The increased focus on therapies for chronic and degenerative diseases will only make clinical research more costly because of the need for complex patient care and associated expenses, larger trial sizes and time frames to confirm efficacy.

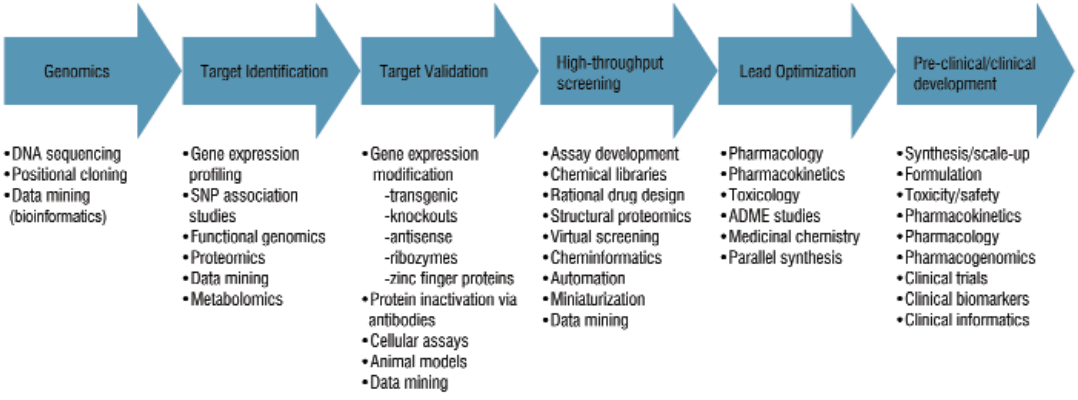
1.2.2 Drug Discovery

Drug discovery is often perceived as a process that proceeds linearly from gene discovery to gene function (target identification) followed by target validation, combinatorial chemistry, high-throughput screening, hit selection, and lead optimization (Figure 2). The efficiency of each of these steps is related to the current level of technology. For example, advances in DNA sequencing have reduced gene discovery as a bottleneck, while ultra-high-throughput screening has enabled researchers to test more than 100,000-200,000 samples a day. The present rate-limiting steps are target validation and target identification.

It is estimated that approximately 100 targets account for all drugs on the market and the sales of the top 100 drugs are based on only 43 targets.[9] The vast majority are based on targets such as enzymes, G-protein-coupled receptors, and protein kinases. A wide variety of diseases are influenced by ion channels but only a few have been commercially exploited as targets because of a lack of structural information and bottlenecks in high throughput assay technologies. This target class offers opportunities for the treatment of chronic pain, addiction, anxiety, schizophrenia, and Parkinson's amongst others. Target identification is particularly challenging in neuroscience because of the brain's complexity.

Metabolomics, RNA interference, and chemical genomics are being used to address bottlenecks in target validation, while stem cells and system biology are potential target identification tools. Biomarkers for patient stratification in clinical trials will further reduce the risks associated with new targets. New screening and lead optimization strategies include microwave organic synthesis of chemical libraries (large, hypothetical databases of chemical structures), high content screening and *in silico* modeling technologies to guide lead selection and optimization, and earlier prediction of ADMET characteristics (absorption, distribution, metabolism, excretion, and toxicity) using, for example, stem cells.

Figure 2: The Genomics-based Drug Discovery and Development Process



Source: Decision Resources Inc., "Advances in High-throughput Screening—Do They Lead to New Drugs?," Drug Discovery and Design, October 2003.

[9] U. Betz, "How many genomic targets can a portfolio afford," Drug Discovery Today (Aug. 2005), p. 1059.

Target Validation

Target validation refers to the determination that a protein target is crucial to the disease process, that modulating the target with a small molecule drug or monoclonal antibody will likely have a therapeutic effect, and any such effect be dose-dependent. The newer targets being discovered through genomics have suffered from insufficient study of the underlying biology, especially the complexities surrounding cell signalling pathways in contrast to the older targets whose role in the disease process were relatively well understood.

Mammalian models, particularly the mouse, have traditionally been employed to validate drug targets. Strains with mutations or deletions in specific genes are created using classical genetic knockout techniques to determine the effects of the gene's altered activity in specific tissues. The process is expensive, however, and cannot be performed in a high-throughput manner.

RNA interference. Faster knockdown techniques using *antisense* and more recently RNA interference (RNAi)[10] are being applied in lower organisms such as nematodes, fruit flies, and zebra fish,[11] which are susceptible to high-throughput analysis. RNAi not only has the potential of industrializing *in vivo* target validation and identification, but the molecule can then be converted to a therapeutic agent that blocks the gene's expression. However, a number of challenges in delivery, poor tissue distribution, off-target silencing, and variability in the degree of knockout between genes have to be resolved before it can be used as a therapy.

Bacteriophages have long been viewed as potential antibacterial therapeutic agents because they can develop unique proteins that inactivate critical cellular proteins. However, they can also be used as high-throughput screens to identify and validate antimicrobial small molecules against phage-validated bacterial targets. These small molecules could be cheaper and more effective than traditional antibiotics.

Metabolomics. Many genetic knockouts (deletions) in cells or model organisms produce no obvious change because of redundant molecular pathways, making functional studies of these genes difficult. Metabolomics is the identification of metabolite profile patterns (e.g., lipids, sugars, amino acids, and hormones) in biological fluids or tissue samples that result when their normal state is disturbed by disease or drug therapy. The precise measurement of changes in metabolite concentrations may be used to define the function of unknown genes, to identify the critical enzymes or proteins involved, to build a biochemical hypothesis of the disease process, and to validate drug targets by measuring the effects of the drug compound. Metabolimics is also expected to underpin systems biology by providing insights into the interconnected molecular pathways in cells and organisms. For clinical development applications, changes in metabolic profiles could yield biomarkers for potential toxicity as well as markers for screening and monitoring clinical trial patients.

Nevertheless it will take a number of years before metabolomics has a major impact on drug discovery as it is highly dependent on the development of new bioinformatic tools necessary to wade through vast databases.[12]

[10] In RNAi, a double-stranded RNA segment is introduced into cells or organisms to silence a specific gene by binding to and initiating the degradation of the gene's mRNA.

[11] Because each organism lack some of the characteristics of human physiology, more than one model is necessary for better human predictive ability.

[12] Metabolic responses, for example, are affected by variables such as proteins, diet, and age that may mask the effects of disease; as well, the number of different metabolites is unknown — estimates range from 2,000 to 20,000.

Also, existing detection instruments (mass spectrometry, nuclear magnetic resonance spectroscopy, liquid/gas chromatography) need improvements in throughput, sensitivity and degree of multiplexing as well as better technologies for sample handling and preparation. Several European research groups (Imperial College, BioCentrum Amsterdam, the Max Planck Institute) have active research areas in metabolomics and it is also a major element of the US National Institutes of Health (NIH) medical research roadmap.

Chemical Genomics. Even if a target has been validated, it may not be druggable,[13] because it may not have pockets of the right size, shape, and physicochemical and electronic properties to bind small molecules with high affinity and specificity. An alternative target in the disease pathway might instead be superior. Some pathways, such as protein-protein interactions, are widely regarded as undruggable[14] because of the broad structure of the interface site. There are no small molecule drugs on the market (with the exception of a handful of natural products) that target protein-protein interactions. Other target classes that may not be druggable include vascular endothelial growth factor (for colorectal cancer) or tumour necrosis factor alpha (for inflammatory diseases). These are presently being addressed with recombinant proteins or monoclonal antibody-based drugs which are much more expensive to manufacture and must be taken by injection. Because protein-protein interaction pathways are critical to many biological processes, they are very attractive drug targets for small molecules, sparking increasing research interest in this area.

The number of druggable targets is much smaller than the human genome which consists of around 22,300 genes. It is estimated there are 480 targets yet to be exploited for small molecules, 1,800 more for protein therapeutics, and an additional 2,100 targets for gene therapy and siRNA therapeutics.[15] In addition, there are thousands of potential protein targets for infectious disease from microbial and parasitic organisms of which only about 30, for example, are targeted by current prescription antibiotics. Rather than following the traditional pharmaceutical strategy of starting with the target to find the drug, chemical genomics or chemical biology instead uses particular chemical probes with known biological activities to perturb a biological system (e.g., a cell-based assay) in an attempt to discover the specific target and pathway that are modulated by the chemical. In this approach, gene function and target validation are placed after high-throughput screening, allowing druggability to be determined earlier. The small-molecule compounds generated can be used both as tools to probe biological mechanisms and as leads for drug property optimization. Technical challenges include developing new computational tools and data mining methods for the design of diverse compound libraries, and devising new screening technologies such as small-molecule arrays, protein arrays, and cell-based functional assays to identify inhibitors. The NIH recently launched a major effort in this area.

Target Identification

Stem cells, unspecialized cells that can differentiate into numerous types of specialized cells with specific function, have potential applications in cell therapy and regenerative medicine. They are also being used in drug discovery for understanding disease mechanisms and identifying targets, for improved screening

[13] There is a difference between druggability and biological activity. A protein may be druggable but modulating its function with a small molecule may have limited therapeutic value. On the other hand, a protein may have an important role in the disease process but may not be druggable.

[14] Protein-protein interaction pathways found in apoptosis, the major pathway of programmed cell death (cancerous cells, for example, exhibit unchecked cell growth caused by the lack of apoptosis) have no known druggable targets. This has resulted in the use of an alternate strategy based on antisense apoptosis inducers, but these agents have drug delivery problems.

[15] U. Betz, "How Many Genomics Targets Can a Portfolio Afford," Drug Discovery Today (August 2005), p. 1061.

assays, and in toxicology and metabolism studies. An understanding of the genetic pathways that direct stem cells to expand, migrate and differentiate could result in the identification of targets that can be manipulated with small-molecule drugs. The cells' differentiation process involves several key steps, which can serve as targets for drugs to produce specialized cells that will mitigate disease.

Therapies may be based on the molecules secreted by stem cells as well as the cells themselves. Examples include the manipulation of cardiac stem cells with therapeutics to regenerate heart muscle cells, or drugs that can stimulate stem cells to regenerate neurons in Parkinson's disease. The source, stability, and growth of stem cells and their derived cell lines are major challenges. There is also a need for more researchers trained to culture and manipulate stem cells.

Epigenetics. This is the study of inheritable changes in gene function that occur without alterations in DNA sequence. Three systems are used to initiate and sustain epigenetic gene regulation: DNA methylation (a process in which an enzyme attaches a methyl group to DNA), RNA interference or silencing, and histone modification (histones are a family of proteins associated with DNA). Disruption of one or more of these systems can lead to inappropriate expression or silencing of genes. Epigenetics is especially important in cancer and diseases related to aging. Understanding the molecular mechanisms has led to the identification of novel targets for anticancer drug development. Most commercial interest has focused on developing inhibitors of DNA methyltransferase (DNMT) and histone deacetylase (HDAC) enzymes (e.g., Methylgene, Montreal for the latter). Not all tumours or all patients will necessarily benefit from epigenetic therapies, so the field will probably require the development of companion diagnostic products. The optimum treatment strategy may include a combination therapy; i.e., both a DNMT and an HDAC inhibitor.

Systems Biology. Drug discovery has traditionally focused on understanding the function of one component of a biological system at a time, such as an individual gene or protein and the modification of a single target. However, genes usually do not work alone but function within a system of interdependent networks or pathways. Systems biology is the study of the multiple interacting components that govern biological network behaviour under dynamic conditions using mathematical modelling based on experimental data. It attempts to understand and predict a particular system's behaviour, be it cell, tissue, or organ, before and after a disturbance (e.g., a drug injection). The approach can identify new "wet" experimental strategies, after which the models can be refined in an iterative fashion to account for new test results.

In the short term, systems biology will be used to select drug targets and drug development candidates including biomarkers for efficacy and toxicity. Longer-term goals are to simulate disease states in "virtual patients" to predict the effects of "virtual" drugs and to optimize clinical development. Systems biology can also lead to the design of new and improved biological functions not found in nature via "synthetic biology". Because of the complexity of biological systems, current efforts are limited to simple organisms or specific pathways. Examples include:

- a G-protein coupled receptor model for simulating a signal transduction pathway;
- a mechanism of heart failure;
- bioequivalence trials for a controlled dosage formulation;
- a liver cell to simulate toxicological tests;
- a model of glucose metabolism used in the design of Phase I trials for a type 2 diabetes drug;

- the role of phosphodiesterase as a potential drug target for asthma;
- a model of antibiotic resistance in *E. coli*; and
- a model of electrical activity in the human heart designed to evaluate drugs that might trigger QT prolongation.

The US has a significant targeted investment program in systems biology; several other countries [e.g., Germany (liver cell) and Japan (computer modelling)] have also initiated national programs. The field is dependent on the availability of better metabolic profiling technology, real-time imaging techniques at the single-cell level to improve measuring, robust and faster simulation algorithms, and increased computing capacity to link diverse biological data sources of different types. Common standards will facilitate the exchange of predictive tools, models and simulations and the design of suitable databases to file these data. Intellectual property (IP) policy will also have to be clarified; otherwise, there is a risk of multiple patents being filed on a particular system's components by various researchers. This could inhibit commercialization due to potential infringement suits or complicated licensing arrangements.

Glycobiology (Glycomics). Comparatively simple post-translational modifications to proteins such as phosphorylation or acylation have been targeted extensively for drug discovery. However, the greatest structural and functional diversity of proteins is created by a more complex modification termed glycosylation, the attachment of carbohydrate structures known as glycans. Many biological processes — cancer transformation, pathogen recognition, immune system regulation, tissue repair, and anti-infection responses — involve carbohydrate-receptor binding. Because of their important roles in many disease processes, carbohydrate-based molecules and their interactions are potential targets for drugs that can interfere with carbohydrate-processing enzymes, cell adhesion, etc.

Examples of the application of glycosylation in drug discovery include a malaria vaccine based on a toxin identical to the one produced by *Plasmodium falciparim*; neuraminidase and selectin inhibitors; glycosyl and sulfotransferase inhibitors; an HIV vaccine based on the 2G12 epitope of HIV gp120;[16] and a glycopeptide anticancer vaccine containing five antigens. Despite these examples, the study of carbohydrate biology has largely been neglected in drug development due to their complex molecular structure (sugars exist in branched forms rather than the linear form of DNA) and the lack of high-throughput analytical tools and methods. This knowledge gap makes it very difficult to define their molecular structures and monitor how they interact with receptors at the cell surface and elicit biological effects.

A number of recent advances have simplified and accelerated carbohydrate synthesis and analysis. Proprietary enzymes, combined with tools such as nuclear magnetic resonance (NMR) and mass spectrometry (MS) and unique computational algorithms, have been used to determine the specific sequences contained in the sugar chains and the manner in which the various building blocks are linked. It has thus been easier to identify sugar structures, correlate them to biological activity, and engineer improved drug candidates with higher levels of bioavailability. A carbohydrate-spotted microarray — a "glycochip" — has been developed to identify which sugar structures bind to a protein, characterize novel carbohydrate binding proteins, identify new chemical entities as potential inhibitors of glycan-protein interactions, or analyze immunogenicity by assaying serum samples of antibody-glycan binding.

[16] T. Creavin, "Antigen synthesis opens the door to a broad spectrum AIDS vaccine," Drug Discovery Today (June 2004), pp. 507-508.

Still lacking, however, are high-throughput tools for determining the sites of carbohydrate attachment to the protein backbone and methods for obtaining diverse carbohydrates for immobilization and study. The complex structure of oligosaccharides has made classical synthesis unfeasible, but several novel methods have recently been commercialized. They range from Ancora Pharmaceuticals' solid phase synthetic methodology, Optimer Pharmaceuticals' programmable one-pot solution phase technique, to Applied Biosystem's oligonucleotide synthesizer, which has been adapted to generate a complex hexasaccharide. Much of the basic research in glycobiology is undertaken in academia, and several public glycomic initiatives have been established in the US, Japan, Denmark, and the UK to move the basic technologies forward.

New Strategies in Vaccine Research. The ability to sequence bacteria has revolutionized vaccine research, enabling the identification of potential vaccine candidates without the need for cultivating the pathogen or its components *in vitro*. The previous approach was not only time consuming but failed to deal with pathogens that do not grow *in vitro*; it also only enabled the identification of the most abundant antigens, while the most antigenic proteins may be expressed at very low levels.

"Reverse vaccinology" involves the *in silico* analysis of microbial genome sequences followed by the expression of the genes of interest, with the most immunogenic proteins used for development. This strategy enables researchers to focus on the most promising candidates from a large number of antigens for more rapid development at less cost. It was first applied to identify potential antigens for a vaccine against meningococcus B, then for vaccines against group B streptococcus, chlamydia and the hepatitis B and C viruses. The technology could dramatically reduce the time needed to construct influenza seed viruses. Furthermore, vaccines against pandemic threats such as the H5N1 virus can only be generated by reverse genetics.[17]

A long-term strategy for influenza is the development of a "universal" vaccine (e.g., Variation Biotechnologies, Quebec) based on invariant regions of the virus, which would be effective against all circulating strains of both influenza A and B, a medical and manufacturing breakthrough if successful. Most research is focused on the ion channel matrix protein 2 (M2) because of its limited antigenic change compared to two other glycoproteins on influenza's viral envelope, hemagglutinum (HA) and neuraminidase (NA). However, such a vaccine would only be effective against influenza A as M2 is not present in influenza B strains. Another approach involves the relatively conserved subunit region of HA, the HA1/HA2-joining region, which could be used for influenza B. Both strategies do not yet provide the level of protection provided by current vaccines when tested in animal models. Considerable work is still required on increasing the immune response.

A new technique can potentially overcome difficulties in characterizing surface proteins and expand the range of antigens used in vaccines. The method involves treating bacterial pathogens with enzymes to selectively digest protruding surface-exposed proteins. These are subsequently identified by a combination antigens.[18]

[17] P. Palese, "Making Better Influenza Virus Vaccines," www.medscape.com/viewarticle/518514, accessed December 21, 2005.
[18] Manuel J. Rodriguez-Ortega et al, "Characterization and Identification of Vaccine Candidate Proteins through Analysis of the Group A Streptococcus Surface Proteome," Nature Biotechnology (February 2006), p. 191.

There is increasing evidence that infectious agents are a major contributing factor in the development of certain cancers (e.g., papillomaviruses for cervical cancer) and play a role in coronary artery disease, autoimmune disorders such as multiple sclerosis and diabetes, and transplant rejection. This is stimulating research in the identification of these agents and the corresponding immune response mechanisms in order to develop therapeutic vaccines for chronic diseases. The Canadian Network for Vaccines and Immunotherapeutics had expertise in the cancer area, but its funding was not renewed beyond 2007.

Vaccination has been directed mainly at infants and children, but new populations are now being targeted: adolescents, adults, the elderly, pregnant women, individuals with non-infectious diseases, and individuals with chronic infections. Little is known about immune regulation at the different stages of human development, the human immune response to chronic infection, and the role of T cells in vaccine-induced immunity.

Combinatorial Chemistry, Screening and Lead Optimization

Combinatorial chemistry involves the synthesis of thousands of chemical compounds. Starting with a core molecule, different chemical groups are added (based on random selection, predicted drug-like properties, computational analysis, or previous literature results), resulting in molecules with different pharmacological properties. The technology is defined by the type of reaction (solid phase or liquid phase) and the techniques used to control chemical diversity (parallel synthesis or split-and-combine synthesis).

A recent major innovation, *microwave-assisted organic synthesis*, permits the rapid generation of compound libraries in minutes instead of hours or days. Reproducibility is superior and purification protocols are simplified by reduction in unwanted side products. It is also useful in carbohydrate chemistry synthesis and in uncovering new chemical reactions. Efforts are also being made to introduce diversity into library synthesis, since chemical and structural diversity are as important as library size. One approach is to alter the core structure of the starting molecule instead of the functional groups. DNA shuffling is also used to create new biologically active molecules for the generation of natural product libraries, because natural products provide more structural diversity than synthetic compounds.[19]

Screening Trends. In high-throughput screening, large libraries produced via combinatorial chemistry are screened against drug targets to identify which bind to the target or inhibit a particular reaction. These "hits" enter secondary screens to check for properties such as toxicity and solubility, and the lead compound(s) generated are then optimized through medicinal chemistry[20] and taken to early-stage development.

However, the process has added to drug discovery costs for a variety of reasons:

- high investment for infrastructure, e.g., detection methods, robotics, screening assays (typical screens cost $100K to $1M), and informatics software;
- very low hit rates due to the unsuitability of biochemical assays in screening two major

[19] Christopher Dobson, "Chemical Space and Biology," Nature (December 2004), p. 827.
[20] The synthesis and retesting of analogues to ensure the compound has acceptable pharmaceutical properties in terms of potency, bioavailability, and high affinity and selectivity for the biological target.

drug targets — G-protein coupled receptors (GPCRs) and ion channels;[21]
- the inability to optimize the leads identified through medicinal chemistry;
- the hits identified often belong to known drug classes, which cannot be patented; and
- small molecules cannot address undruggable targets such as protein-protein interactions.

The growing shift to functional cell-based assays allows screening under more physiological conditions, providing more information from each test. Strategies include:

- multiplexed assays using multiple different cell lines or different targets in a given well to reduce reagent cost and increase speed;
- assays than can screen across many different target classes;
- replacement of traditional plate-based systems with microfluidics;
- new technologies such as microfluidic chips to increase the efficiency of patch clamping for ion channel screening; and
- simultaneous analysis of drug targets with absorption, distribution, metabolism, excretion and toxicity (ADMET) markers in single wells.

Approximately half of development failures (costing nearly US$70M) are due to poor ADMET properties. Those that do get to market may have suboptimal properties or risk being pulled (e.g., Vioxx) because of safety concerns that only surface after the drug reaches the market. Testing is usually undertaken during the lead optimization stage because of cost (fewer compounds need to be examined) and the low throughput of *in vitro* human cells, tissues, blood proteins or animal models used. There is also a belief that poor properties can be modified later with medicinal chemistry but, as noted, this is not necessarily successful.

Early prediction of liver, cardiac, kidney, and central nervous system (CNS) toxicities is of critical importance. According to the Tufts Center for Drug Development, three therapeutic classes — cardiovascular, anesthetic/analgesic, and anti-infectives — accounted for 70% of drug withdrawals between 1980 and 2005, with 50% of these being due to cardio/renal effects and 40% due to liver toxicities. Drug-induced QT prolongation[22] has led to the removal of at least five drugs since 1999 and "black box" warning labels being issued for several others. Drugs/indications with a high risk factor of QT prolongation include antivirals and antibacterials where high plasma concentrations of the drug are necessary to suppress resistance; pain management and anti-psychotics where overdosing is likely; and drug-drug interactions via P450 metabolism, which may lead to high drug plasma levels. Efficacy for CNS drugs depends on being able to readily penetrate the blood-brain barrier, but other drugs must be non-permeable to minimize CNS toxicity.

Promising assays and tools to increase the throughput and predictability of ADMET screening include stem cell-derived hepatocytes[23] for metabolism assays, engineered cell lines that express drug-

[21] GPCRs must be screened in a cell-based format to mirror the *in vivo* environment, while screening methodologies for ion channels (the "patch-clamp" technique, which measures ionic currents under a defined membrane voltage) are extremely low throughput, require technically skilled operators, and are difficult to scale up. Ion channel libraries also do not benefit from as wide a chemical diversity and number of known ligands to use as a starting point as GPCRs.

[22] An abnormality of cardiac muscle repolarization, defined as the time from Q wave deflection to the end of T wave on an electrocardiogram.

[23] Because a drug's safety and efficacy often depend on how it is metabolized in the liver and whether toxic or inactive metabolites are generated, assays are based on hepatocytes (liver cells) harvested from cadavers, but human liver tissue is expensive and difficult to obtain.

metabolizing enzymes for predicting drug-drug interactions, and assays based on zebra fish as predictive toxicity screens that can be used in a high-throughput format.

High-content screening (HCS) can convert hits to leads more efficiently (i.e., improve the quality of the lead candidate by identifying those compounds most likely to succeed). HCS involves the use of probes and various imaging techniques to visualize individual cells and measure the multiple effects of a drug candidate (e.g., inhibition of a binding event, apoptosis, selectivity, toxicity, cell permeability) on various pathways within an individual cell over an extended period in a single assay. Applications include target validation, assay development, *in vitro* cytotoxicity assessment, and prioritization of lead compounds. However, the technology is expensive, suffers from relatively low throughput, and is more challenging than high-throughput screening based on biochemical or cell-based assays. Needed improvements include better multiplexed assays for measuring multiple cellular targets and processes in numerous cell types; more efficient methods for extracting and analyzing the image data generated; brighter, smaller, and more sensitive molecular probes able to follow dynamic cellular processes within cells without disrupting cell components; and better artificial intelligence and pattern recognition software.

In silico tools such as **cheminformatics**, computer-aided drug design, and virtual screening are also being used to guide the selection and optimization of drug leads. Cheminformatics involves the computer-assisted selection of chemical structures that are highly correlated with bioactivity from a large data set for more focused synthesis and testing. Selection methodologies include similarity to known drugs and **virtual screening**, the use of docking and scoring algorithms to predict the binding affinity between a target protein and a virtual library. Predictive accuracy is constrained by the lack of experimental data (e.g., accurate protein structure), inaccessible databases (cheminformatics databases are usually privately owned or are not properly organized), and inefficient docking algorithms.[24]

Another tool that is a more rational approach to drug discovery than random compound screening is **structure-based drug design**.[25] Knowledge of the protein's 3-dimensional structure can lead to the design of drug molecules that precisely fit the binding sites of protein targets and in antibacterial discovery to determine the structures of proteins of uncharacterized function as potential targets for new antibiotics. Although several drugs (e.g., the HIV-protease inhibitor Viracept™ in 1997) were brought to the market as a result of structure based drug design, cost and low throughput restricted the technique mainly to the lead optimization stage to improve potency or selectivity. Recent breakthroughs[26] in the industrialization of protein structure determination combined with tools such as virtual screening have made it possible to apply it earlier in the process.

[24] More accurate algorithms that consider the flexibility in the torsion angles in both the protein and small molecule will better predict how the two will interact. More rapid algorithms and more computing power are needed if large libraries are to be screened in a reasonable time. Present scoring functions cannot rank subtle differences between ligands or model side effects properly.

[25] X-ray crystallography, nuclear magnetic resonance or homology modelling are used to calculate the 3-D structure of a target protein. Computer algorithms are then employed to calculate the likely binding sites for molecules and to select compounds from a database with appropriate molecular shapes and functions. These compounds are positioned into regions of the protein structure and ranked based on their electrostatic interactions with the target site to alter the protein's biological activity.

[26] Advances include the use of liquid handling dispensing robots, the ability to dispense protein nanodroplets (which has led to more rapid appearance of crystals), the availability of much more intense synchrotron beam lines suitable for analysing these very small crystals, and crystal mounting and alignment robots enabling unattended collection of X-ray data 24 hours a day.

An important trend is the use of X-ray crystallography or nuclear magnetic resonance for fragment-based screening. Weak binding low molecular weight molecules having one or more functional groups can be easily identified compared to traditional bioassays which are not suitable for revealing low-affinity compounds. The different fragments that bind to the site can then be linked to produce a new compound with higher affinity and lower molecular weight than developed through conventional combinatorial chemistry and lead optimization techniques.

The short-term strategy is to use structure information of potential drug receptors to design more focused libraries to guide lead selection and optimization (e.g., Chemical Computing Group, Montreal). The long-term goal is the *in silico* prediction of ADMET properties based on chemical structures alone to filter out those structures that have an unwanted side effect (different variants of a particular protein receptor could lead to variations in drug response).

Although current models have poor predictive capability due in part to limited toxicity and pharmacokinetic data, this is expected to improve with the recent introduction of automated high-throughput patch clamp technology for ion channel screening. Active research areas include the *in silico* modelling for hERG sodium and potassium channel blockers implicated in QT prolongation by understanding structure-activity relationships governing hERG-drug interactions[27] and the development of an *in vitro* blood-brain barrier model that can predict drug permeability. (The Chemical Computing Group offers software for predicting blood-brain barrier permeability and compound binding to different receptor classes.)

A technology utilizing established transmission electron microscopy in combination with proprietary algorithms can obtain detailed 3D images of individual proteins. Applications include investigation of molecular mechanisms such as the structural dynamics of ion channels or study of flexible proteins, as well as validation of preclinical models and analysis of drug candidates.[28]

According to some estimates, application of computer-aided drug design could lead to savings in R&D costs between target selection and filing of an Investigational New Drug Application of up to 50%,[29] but it could take 10 years before it becomes widely applicable across a range of targets. Challenges include the small percentage of protein crystal structures that have been determined to date, particularly the most important types accounting for over half of all proteins — those bound to cell membranes such as G-protein coupled receptors (GPCRs) — which are almost impossible to crystallize (the only current exception is bovine rhodopsin). Proteins also can take on several shapes that may shift during binding, so that many different structures for a single protein will have to be deduced. Lastly, high-throughput protein expression is a major bottleneck. Only a third of the proteins, for example, are expressed in a soluble form and of these at most 50% yield diffraction-quality crystals.

This problem may be addressed with a microfluidic device — the Topaz™ system — recently launched by US-based Fluidigm or with a newly developed diffraction technique [wide angle X-ray scattering (WAXS) of proteins in solution], which does not involve the growth of the high quality crystals necessary for X-ray crystallography. The latter may also prove useful as a high-speed tool for lead

[27] A.M. Aronov, "Predictive in silico modeling for hERG channel blockers," Drug Discovery Today (January 2005), pp. 149-156.
[28] Sidec Technologies. www.sidec.com.
[29] D. Filnore, "Crystallography on Drugs," Today's Chemist at Work, American Chemical Society (January 2004), p. 32.

identification, as it appears to be sensitive enough to differentiate between a small molecule sticking to a surface of a protein (a drug that may have no effect) and one that is actually changing the protein's structure and functionality (more likely to be effective).

In silico modelling of proteins for improved bioavailability. Many therapeutically potential peptide- and protein-based drugs are abandoned in preclinical and clinical development because of aggregation problems which affect the protein's bioavailability and increase the risk of immunogenic reactions and can hinder production (e.g., insulin tends to form fibrils during production, storage and delivery). Algorithms using a polypeptide's physicochemical properties can be applied to predict the effect of amino acid substitutions to design bioactive analogues *in silico* with a reduced propensity for aggregation and higher bioavailability than natural sequences, and to optimize formulations and shelf life of many existing protein drugs.[30] Their application in the search for drug inhibitors of aggregation, an underlying component of diseases such as Parkinson's (Lewy bodies), Alzheimer's (beta-amyloid plaques), and Huntington's (mutant huntingtin proteins), would also be a major drug discovery breakthrough.

Metabolomics. This can prioritize lead compounds by revealing correlations between particular metabolic "fingerprints" and an organism's specific physiological states. Compounds that elicit profiles previously determined to be relatively innocuous can be prioritized over others. For clinical development applications, changes in metabolic profiles could elucidate disease mechanisms and yield biomarkers for early disease prediction, detecting potential toxicity as well as screening and monitoring clinical trial patients.

Synthetic Biology. The technology involves the design of "artificial" biological molecules through cycles of computer modelling using biological functional rules to obtain new functionalities not present in nature. A recent example (Lawrence Berkeley National Laboratory) is the development of a much less expensive process for the production of the antimalarial drug artmisinin, a natural product presently extracted from the leaves of the sweet wormwood tree. This was achieved by adding new genes and engineering a new metabolic pathway in *E. coli* bacteria to synthesize the artmisinin precursor amorphadiene. In another case, researchers at Howard Hughes Medical Institute used computer algorithms to design and synthesize a protein with a desired folded structure that could open the way to engineering proteins with specified functions. This emerging field raises concerns about how modified organisms might fare in the environment and the risks of bioterrorism resulting from the production of new strains of bacteria.

Nanotechnology-Based Research Devices

Advances in research tools and instrumentation, such as gene sequencing, PCR (polymerase chain reaction), microarrays, mass spectrometry, and various imaging techniques and contrast agents, have combined with increased computing power and miniaturization to fuel drug discovery R&D. Nanotechnology[31] offers the potential to develop a new generation of analytical devices for basic

[30] Susan B. Fowler et al, "Rational design of aggregation-resistant bioactive peptides," Proceedings of the National Academy of Sciences (July 19, 2005), pp. 10105-10110. Similar work is being undertaken at the SWITCH Laboratory at the University of Brussels.

[31] Nanotechnology is the manipulation and interaction of materials measuring 100 nanometers (nm) or less in at least one dimension. One nm is one billionth of a meter; the diameter of a human hair is 50,000 nm, red blood cells 7,000 nm, a bacterium around 1,000 nm, viruses roughly 100 nm, receptors about 5 nm in diameter, quantum dots 2-9 nm, DNA 2.5 nm, an aspirin molecule 1 nm, a water molecule almost 0.3 nm across, and a typical bond between two atoms 0.15 nm long. The properties of materials can be different at the nanoscale because of their relatively larger surface area and because quantum effects begin to dominate the behaviour of matter affecting optical, electrical, and magnetic properties.

research that have significantly improved signal generation and detection capability and smaller sample size requirements.

Atomic force microscopy (AFM), a well-established tool used to measure nanoscale surface features in semiconductors, is now able to measure forces in biological processes and to initiate intracellular signalling. Continued advances in instrumentation and techniques (for example, by coating the AFM tip with an antibody or small organic molecule) have resulted in an ever-increasing number of novel applications, with more expected to emerge in the future. AFM has been used to compare the effects of different molecules on inhibiting the formation of insoluble plaques associated with Alzheimer's, and in cancer research to study the timing at which cancer cells decrease in height and volume when exposed to an apoptosis-inducing agent. A new technique called force volume imaging or affinity mapping (the AFM-coated tip creates a force curve as it approaches and retracts from different positions across a cell) can identify the distribution of target molecules on the cell surface or study changes induced by drugs on the mechanical properties of cell membranes. Other applications of AFM include imaging living cell features that traditional optical methods have been unable to capture, such as the detailed structure of neuronal processes, or monitoring intracellular calcium signalling[32] to determine how osteoblasts (bone forming cells) sense and respond to strain and how mechanical forces (exercise) can affect their growth.

In the area of screening and lead optimization, magnetic nanoparticles combined with magnetic resonance imaging have been developed for rapid screens of telomerase activity for target identification in cancer. Nanoscale cantilevers can detect the presence of a particular genetic sequence or other molecules for target validation, ADMET screening, and metabolism studies (binding with a complementary molecule induces a bending stress that can be measured using laser interferometry). Other examples include a nanofluidic system for crystallizing proteins that cannot be grown with conventional technologies; DNA scaffolds or cages that organize proteins for crystallography experiments; nanowire devices that analyze the specific binding of small molecules to proteins for drug discovery and screening; and gold nanoparticles coated with oligonucleotides (nano bar codes) for ultrasensitive detection of biomarkers.

Microarrays and microfluidic chips will be replaced by the next-generation miniaturization technologies, nanoarrays and nanofluidics. Nanoarrays are ultra-high-density gene chips with 100,000 spots of DNA in the area occupied by a single spot in conventional microarrays; this level of ultra-miniaturization will require additional developments in dip-pen nanolithography as well as novel signal processing techniques that can discriminate a weak signal from background noise. Also in development are higher density protein arrays. Microfluidic chip platforms (the so-called lab-on-a-chip) integrate a chemistry lab on a small substrate using micro-electromechanical systems (MEMS) to manipulate and analyze liquid volumes. The sensitivity can be enhanced by creating nano-electro-mechanical systems (NEMS) and structured surfaces and channels. Applications can be expanded to include analyzing individual molecules such as target oligonucleotides, sequencing strands of DNA and RNA (for example, by correlating changes in the electric current that flows through the pore as the single-strand DNA molecule passes through the opening), and increasing the number of screening experiments. Edmonton-based Micralyne is a leading microfabrication company supplying MEMS-based products such as biosensors, chips for sequencing, and imbedded drug delivery devices to a variety of industries.

[32] Signalling occurs both when the AFM tip contacts the surface (creates strain) and when it is withdrawn.

Nanoparticles such as quantum dots (QDs, nanocrystals of semiconductor material), gold colloids, luminescent dendrimers, nano bar codes (QD-embedded coloured polymer microbeads), and nanoshells (gold-layered dielectric nanoparticles with tunable optical resonances) are being evaluated for imaging drug receptors and for screening because of their unique properties. However, no single nanoparticle will necessarily be suitable for every application. QDs have received a lot of attention in areas such as high content screening because of their superiority over conventional organic fluorescent dyes (brightness, narrow emission spectra, broad UV excitation, photo-stability, and multiplexing capability). QDs bind to cell surface receptors without disrupting cell physiology, resulting in a better understanding of the complex signalling networks that govern the behaviour of cells, and helping to identify the mode of action of new drugs. Their longer excitation lifetime enables researchers to image single-cell migration and differentiation in real time over extended periods, an advantage in research areas such as embryogenesis, cancer metastasis, and stem cell therapeutics. They can track multiple molecular targets simultaneously with a single light source (multiplexing), crucial in the analysis of complex diseases such as cancer that involve numerous genes and proteins. Examples include labelling the breast cancer marker Her2, tracking the movements of the erbB family of receptors (a common cancer drug target) on the surface of living cells, and *in vivo* imaging of animal models to determine where drugs are being targeted.

Before QDs (and many other nanoparticles) move to the clinic, concerns about potential toxicity will have to be addressed because of their ability to enter the body through pores and accumulate in cells or lungs. Formal methods have to be established for their characterization in terms of particle size, size distribution, shape, coatings, and surface area to predict which traits would be harmful. Tissue absorbs and scatters light resulting in little light available for QD excitation. Clinical applications will require more efficient and compact excitation and detection instrumentation. Synthesis techniques will also have to be improved to reduce particle size variation, which affects test results, and surface chemistry needs to be refined to minimize particle aggregation. Optical effectiveness needs to be optimized when QDs are linked with several molecules.

With current capillary-based DNA sequencers, it costs well over $10M to sequence the three billion base pairs in the human genome. Sequencing technology needs to become smaller, faster, and less expensive to fulfill the promise of personalized medicine. The US National Human Genome Research Institute's near-term goal is to cut the cost of whole-genome sequencing to US$100K and ultimately to US$1K, which some estimate could be available in 10 years. Breakthroughs in nanotechnology will have a large role in this endeavour. Technologies under investigation include sequencing using nanopores, single molecule nucleic acid detection with nanopipettes, and detection of DNA nucleotide bases by nanoelectrode-gated tunnelling conductance measurements.

The nanotechnology field is dependent on the availability of cost-effective fabrication methods (e.g., soft lithography, molecular self-assembly). Standards are also essential. No universal measurement standards for length have yet been established — even sophisticated atomic force microscopes can produce variations — so it is not possible to compare data across different laboratories. Force measurement standards will also need to improve: control of probe stiffness and geometry is important for accurate measurement of biological materials such as the elasticity or bond strength of protein and nucleotide molecules.

1.2.3 Preclinical/Clinical Development

The number of participants in clinical trials for new molecular entities has grown over the past 25 years, increasing from 2,200 people on average to current levels of 5,600.[33] The trials have also increased in complexity when measured by the mean number of medical/diagnostic procedures applied to patients.[34] The major causes of drug attrition from 1991 to 2000 were efficacy and safety issues, each contributing about 30%.[35] Because a safety issue may occur at a very low statistical frequency (e.g., 1 in 10,000), a problem may not be revealed until after launch when thousands have taken the product. From 1975 to 1999, 10% of approved drugs required safety alerts and seven drugs approved for marketing since 1993 were subsequently withdrawn because they were collectively associated with over 1000 deaths.[36] A 10% improvement in predictability during the clinical phase could save an estimated US$100M in development costs per drug.[37] For vaccines, different infant immunization schedules exist in different countries, driving up clinical development costs; standardization in this area would help bring costs down.[38] The impact of genomics and other technologies on preclinical and clinical development has been relatively small compared to target identification and validation.

Traditional static *in vitro* cell-based assays using isolated cells such as hepatocytes have a number of limitations, with the result that no drug can enter clinical studies based only on *in vitro* screening data. They cannot predict cumulative drug effects during chronic treatment, pharmacokinetic-pharmaco dynamic properties across a range of doses, the effect of the drug on other protein targets, or the interaction of several different cell types on the mechanism leading to toxicity.

Animal models and human clinical trials have been the long-standing tools used to assess a compound's safety profile, but animal models are expensive and labour intensive and the results do not translate well to humans because of genetic, physiological, and immunological differences. Their utility is particularly questionable in the development of drugs for behavioural disorders or disorders with a strong cognitive component. Efforts are underway to reduce the number of animals sacrificed due to the controversial nature of animal research and the increasingly complex requirements for obtaining animal study licences, particularly in Europe. The recently launched US Knockout Mouse Project will create a knock-out mutation in every gene which will be publicly available to build better *in vivo* mouse models. Alternative technologies include computer simulation models of mammalian cells and tissues, *in vivo* micro-imaging systems for non-invasive small animal research such as from VisualSonics (Toronto) or ART Advanced Research Technologies (Montreal), and "cells-on-a-chip" based screening assays capable of mimicking, for example, the vascular system, the liver or the endothelial cells that form the blood-brain barrier (the silicon chip's architecture simulates the way in which cells are exposed to body fluids in different organs).

[33] Clinical trial sizes to confirm safety are much larger for vaccines. Two new rotovirus vaccine candidates enrolled and monitored more than 60,000 infants, making these the largest trials conducted to evaluated vaccine safety.
[34] J. DiMasi et al, "The price of innovation: new estimates of drug development costs," Journal of Health Economics, 22 (2003), p. 177.
[35] I. Kola and J. Landis, "Can the pharmaceutical industry reduce attrition rates," Nature Reviews Drug Discovery (August 2004), p. 711.
[36] Albert Pi Li, "An integrated, multidisciplinary approach for drug safety assessment," Drug Discovery Today (August 16, 2004), pp. 687-88.
[37] Dr. L. Crawford, Acting FDA Commissioner, Speech before the Mayo Alliance for Clinical Trials Conference (August 26, 2004).
[38] J. Kaper et al, "Vaccine Development: Current Status and Future Needs," Report from the American Academy of Microbiology (March 2005).

Testing of vaccines have relied on small animal models and more expensive primates. There are no adequate *in vitro* models of the human immune system. The Rapid Vaccine Assessment Program of the US Defense Advanced Research Projects Agency (DARPA) is funding the development of an artificial immune system on a microfluidic chip using human cells and tissues, which will be able to test new vaccine antigens, formulations and adjuvants.

Toxicogenomics. This is the study of the impact of compounds on an organism, tissue or cell culture to identify changes in gene, protein and metabolomic expression patterns. The resulting profile can then be compared against those in a reference toxicity database. Applications include reducing the need for costly animal testing, prioritizing drug candidates, and identifying persons who are genetically susceptible to the toxic effects of specific drugs in order to exclude them from clinical trials. Current toxicology assessment time for a drug that reaches the new drug application stage is around two to three years and the cost is $2 to $3M; an effective toxicogenomics program could lead to substantial savings.[39] Major challenges include lack of standardized platforms and software for data analysis, limited access to toxicogenomic databases, characterization of specific organ toxicity signatures, and the need for regulators to accept toxicogenomic results as part of toxicology data supporting drug applications.

Human Microdosing. Poor pharmacokinetic (PK) properties such as clearance, distribution, and half-life account for up to 40% of failures in Phase I despite extensive preclinical screening using *in silico* or animal models.[40] Human microdosing can lead to better prediction of PK parameters (the technique provides no safety or efficacy data) in six months or less, compared with 12 to 18 months using animal models. The method involves the administration of microgram quantities of lightly radio-labelled drug candidates and the use of ultra-sensitive accelerator mass spectrometry (AMS) to measure parent drug and metabolite concentrations at specific intervals. The concept was validated in early 2005 in a trial sponsored by Roche, Eli Lilly, Schering and Servier); more studies are underway to determine any limitations, such as drugs with high first-pass metabolism.

Biomarkers and Pharmacogenetics. Biomarkers (biological markers) are physiological characteristics (e.g., blood pressure, ECGs), imaging measurements, molecules such as proteins and metabolites (e.g., blood glucose levels, lipids), cells (e.g., CD4+ blood cell counts), or chromosomes, mRNA expression profiles, and single nucleotide polymorphisms (SNPs) that can be unambiguously correlated with the biological mechanisms of a disease and its treatment. The principle of using surrogate markers such as blood pressure, cholesterol, and prostate specific antigen to monitor disease progression and guide therapy has been standard clinical practice for many years. The increasing emphasis on the discovery of better biomarkers that could also enhance R&D productivity is relatively recent. However, there are considerable challenges in validating any biomarker (fewer than 12 cancer markers, for example, have been approved by the FDA over the past 20 years). In addition, the assay platforms used to measure them are still maturing and are not sufficiently reliable.

Markers with improved discriminatory power can uncover potential toxicity problems earlier (e.g., liver toxicity, which affects one in six drugs in development and is an important cause of post-registration drug withdrawal), and rank preclinical candidates by predicted efficacy and side-effects. They may also

[39] Decision Resources Inc., Drug Discovery & Design, Vol. 1, Toxicogenomics (January 2003).
[40] Ian Wilding and Angus Bell, "Improved early clinical development through human microdosing studies", Drug Discovery Today, July 2005, p. 890.

expedite progression from Phase I to Phase II based on quantification of target modulation rather than achievement of maximum tolerated dose,[41] or optimize dose selection in Phase II through the discovery of new pharmacodynamic mechanisms. Markers can also stratify patients for clinical trials, and ultimately direct therapeutic agents at the right population with the right dosage (so-called "personalized medicine"). By selecting the most appropriate patients for clinical trials to eliminate poor responders (efficacy, drug reactions) from the study population, more powerful trials can be designed, improving success rates and significantly reducing trial costs. Estimated savings include a 20% reduction in the number of compounds tested in Phases II and III, and a 10% decrease in the number of patients and 20% decline in time in Phase III trials.[42] Patient stratification and personalized medicine are most advanced in oncology.[43] Caprion (Montreal), MDS Pharma Services (Toronto), Massachusetts General Hospital (a leader in imaging biomarkers), and US-based Gentris Corp. recently formed the Biomarker Alliance™ to offer biomarker services to industry.

Areas in particular need of more reliable indicators of clinical response are oncology, drugs for children, CNS and neurodegenerative disorders, stroke and head injury, and arthritis. In oncology, important research areas include:

- biomarkers for better assessment of therapeutic efficacy than surrogate endpoints such as change in tumour size;[44]
- better classification of tumours and disease staging for clinical trials;
- markers that can detect tumours earlier when the disease is most likely treatable (e.g., non-small cell lung, ovarian and pancreatic cancers) and no metastases have yet formed; and
- markers that can predict chemotherapy resistance and cancer relapse.[45]

A validated biomarker could prove useful in extrapolating adult clinical data to children, which is presently difficult because of differences in physiology, pharmacokinetics, and pharmacodynamics. Present clinical assessment tools for psychiatric disorders suffer from poor precision. The UK's National Institute for Health and Clinical Excellence (NICE) recently questioned the validity of conventional response criteria used to assess the benefits of Alzheimer's drugs. Markers that identify likely responders or individuals with mild cognitive impairment that do not progress to Alzheimer's could reduce the size and timeframe of clinical trials. It is difficult to conduct proof-of-principle trials in stroke and head injury due to the relatively small trial size and the inability to assess and predict final infarct size as end-points for intervention studies. A biomarker that could differentiate very early between hemorrhagic stroke (resulting from rupture of a blood vessel within the brain) and ischemic stroke (resulting from blocked blood flow to the brain) would also help optimize acute stroke management.

[41] Richard Frank and Richard Hargreaves, "Clinical Biomarkers in Drug Discovery & Development," Nature Reviews (July 2003), pp. 566-67.

[42] Jeffrey Ross et al, "Integration of Molecular Diagnostics with Therapeutics," Medscape.com/viewarticle/447846, Feb. 14, 2003, accessed Dec 12, 2004.

[43] Genentech's monoclonal antibody Herceptin™, which targets the 25–30% of breast cancer patients that overexpress the HER2/neu antigen, was the first targeted therapy linked to mandatory testing of a specific biomarker. Other examples include Gleevec™ (chronic myeloid leukemia) and Erbitux™ (advanced colorectal cancer).

[44] AstraZeneca's non-small cell lung cancer drug Iressa™, for example, was approved on the basis of 50% tumour shrinkage lasting at least one month but had to be pulled from the US market after it was discovered there was no significant increase in survival, a large percentage of non-responders, and a statistically high incidence of interstitial lung disease.

[45] Tumours recur in many early-stage colorectal cancer patients, for example, due to missing pieces of chromosomes 8 and 18. An assay that could measure this imbalance in the clinic would be useful.

Diagnosing an arthritic disorder, particularly in its early stages, is very challenging. A biomarker that predicts joint erosion would enable physicians to identify which rheumatoid arthritis patients should receive aggressive therapy earlier, or the 30% of patients who may not respond to existing biologics. Osteoarthritis is characterized by cartilage loss leading to joint destruction. Conventional radiography is limited in its ability to image cartilage directly. The improvement of osteoarthritis therapies requires devising better methods to view treatment response, and two Canadian companies are involved to date: Arthrovision (Montreal) has developed magnetic resonance imaging (MRI) technology to track cartilage volume and thickness over time, while ChondroGene (Toronto) is developing biomarkers in collaboration with Pfizer. Transplant tolerance, the ability to recognize a transplanted organ as "self" to eliminate immunosuppressive drug therapy, has been the ultimate goal of transplant surgeons;[46] biomarkers could provide an early warning for rejection episodes in the investigation of new tolerance strategies.

Molecular imaging is the use of quantitative functional imaging technology combined with novel targeted contrast agents to look at molecular pathways *in vivo* to assess a drug's interaction with a target or to monitor disease response. In contrast to gene expressions and proteomic patterns, imaging modalities such as functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS), combined with novel targeting contrast agents, provide real-time structural and functional assessments of therapy, enabling direct association between therapy and effect.[47] This property is particularly useful in neuroscience, where surrogate efficacy measures are often lacking, and trial endpoints may be confounded by high placebo response and can take a long time to collect. Molecular imaging is also a promising tool in the development of anticancer drugs by providing information about tissue pharmacokinetics, access to the target organ, and unexpected accumulation in other organs. Other examples of imaging biomarkers include bone-cartilage contrast ratio/MRI for osteoarthritis, apparent diffusion constant/fMRI for stroke, choline-creatine ratio/MRS for Huntington's, and positron emission tomography/Pittsburgh Compound B (an amyloid-binding radiotracer) for Alzheimer's.[48] However, imaging is expensive, requires expertise, and there is a need to standardize data collection for evaluation. It may have limited clinical trial application in Canada.

The study of inherited differences in drug response resulting from DNA sequence variations (SNPs) is the basis of pharmacogenetics. (Pharmacogenomics is a broader term that includes the genetic basis of disease as well as the genetic determinants of drug efficacy and toxicity, but is often used interchangeably.) Most drugs on the market are effective in only about 40% to 70% of the patient population. Variability in individual response to specific medicines in terms of reduced efficacy or enhanced side effects/toxicity is a serious therapeutic issue. Differences may be due to several factors:

[46] Jeffery Matthews, "New Renal Transplant Registry Targets Immune Tolerance," www.medscape.com/viewarticle/483993, accessed August 5, 2004.

[47] Homer Oien et al, "Using Imaging Biomarkers to Accelerate Drug Development and Clinical Trials," Drug Discovery Today (February 2005), p. 260.

[48] It has recently been discovered that beta amyloid proteins that form plaques in the brains of Alzheimer's patients are also present in the eye lens. Instead of imaging the brain, an infrared laser is directed into the lens and the back-scattered light reveals the amount of protein present.

- mutations in genes that code for drug metabolizing enzymes (pharmacokinetics) — fast metabolizers break down a drug too quickly to be effective in doses designed for the majority of the population, while the drug may reach toxic levels in slow metabolizers. Tm Bioscience, Toronto, is working in this area. The CYP450 enzyme family has been the most extensively studied because of its effect on a large number of drugs and patients;[49]
- mutations in genes that code for target receptors or transporter proteins, which affect the drug's ability to reach and interact with the intended target (pharmacodynamics). Examples are the cholesteryl ester transfer protein that determines the efficacy of provastatin in atherosclerosis, the beta adrenergic receptors that affect sensivity to albuterol in asthmatic children, the serotonin neurotransmitter receptor 5HT2A that affects the antipsychotic drug clozapine, and a polymorphism in a sodium channel gene associated with the choices and doses of anti-epileptic drugs; and
- inadequate classification of disease (e.g., acute myeloid leukemia and acute lymphoblastic leukemia respond differently to treatment, as do subtypes of lymphoma).

The high expectations surrounding clinical applications of pharmacogenetics testing are still largely unmet. Many research studies have focused on genes that code for drug-metabolizing enzymes (pharmacokinetic polymorphisms), but genes that code for target receptors or drug transporters (pharmacodynamic polymorphisms) may be more important. Another factor is that drug effects are usually determined by the interplay of multiple genes rather than by the single polymorphisms traditionally studied. Furthermore, with the notable exception of a rare cancer such as chronic myeloid leukemia, caused when parts of chromosomes 9 and 22 are "swapped", most cancers and many other diseases may be the product of 10 or more genes. Because of the limited sensitivity of a single biomarker, it will be necessary to track multiple markers using gene expression profiling or proteomic patterns. Also, recent studies indicate that drug response may depend not only on genes but on the type of bacteria (at least 400 species are known) that thrive in the walls of the human gut. Finally, drug response and dosing are affected by non-genetic effects (diet, smoking, age,[50] liver and kidney function, and co-administered drugs), which confound statistical analysis.

Only a handful of tests have reached the market, such as tests that define eligibility for targeted cancer therapies,[51] tests to analyze genes that govern drug metabolizing enzymes,[52] or HIV resistance testing to uncover viral mutations in order to optimize HIV therapy (e.g., Bayer's genotyping kit, originally developed by Toronto-based Visible Genetics). However, many of them are not mandatory (the only two protein-based anticancer drugs that require a corresponding diagnostic test are Herceptin™ and Erbitux™) or are not yet reimbursable because the clinical utility (e.g., predictive accuracy, potential for therapeutic adjustment) is still to be demonstrated. The additional costs of genotyping are also an issue.

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[49] The CYP3A group, for example, metabolizes almost 50% of approved drugs (e.g., HIV protease inhibitors, immunosuppressants, calcium channel blockers, cancer drugs), while the CYP2D6 family metabolizes 25% to 30% (beta blockers, anti-arrhythmics, antidepressants, morphine derivatives, and anti-psychotics).

[50] For example, liver size and blood flow to the liver generally decrease in older people, affecting drug clearance. Renal clearance also declines with age.

[51] These include immunohistochemical (IHC) and fluorescent in situ hybridization (FISH) assays for selection of breast cancer patients eligible for Herceptin™ and an IHC assay for selecting colorectal patients for Erbitux™ therapy.

[52] In addition to Roche's AmpliChip CYP450 assay, other examples include a test for mutations in the metabolizing enzyme thiopurine methytransferase due to risk of haematopoietic toxicity in leukemia patients taking mercaptopurine therapy and an assay to detect variations in the gene UGT1A1 that affects the metabolism of the chemotherapy drug irinotecan used in colorectal cancer treatment.

Commercial success hinges not only on the biomarker but also on the assay platform that must be developed and validated to measure it, an expensive, time-consuming process. Platforms could be based on protein-, RNA-, DNA-, or cell-based techniques including ELISA, tissue microarrays, immunohistochemistry,[53] laser scanning cytometry, and protein profiles from gene arrays, antibody arrays, surface-enhanced laser desorption/ionization-time-of-flight mass spectrometry (SELDI-TOF) or quantitative PCR. Many platforms used in research are too expensive for clinical applications, lack reproducibility and standardization, are not reliable for predicting individual cases, or are not sufficiently robust.[54] It could be 15 years or more before pharmacogenetic testing and personalized drugs are commonplace.

Modelling and Simulation. For the preclinical area, a number of commercial software programs are available that can simulate the dissolution and absorption of a new drug in the human gastrointestinal tract, the enzyme-specific metabolism in the liver, and the blood plasma concentration time history to predict pharmacodynamic effects of the drug on the body. In development are models that simulate the distribution of drugs to various tissues such as the brain, heart, lungs, pancreas, muscle, and reproductive organs. Predicting the amount of a drug that reaches different body tissues will enable researchers to more accurately estimate its therapeutic and adverse effects.

Clinical disease modelling (e.g., asthma, obesity, diabetes) can help predict which drug and drug target would have a clinically significant impact. Computer-simulated trials based on preclinical and Phase I data could enable clinical researchers to test their designs, assumptions, and the clinical measurements most likely to predict success in advance of a trial. It could assist, for example, in identifying proposed doses for a Phase II trial, designing the most effective Phase III trial design,[55] or reducing the risk of testing drugs in certain high risk populations such as children. Cost savings from the use of model-based drug development are estimated at 16% to 20%, mostly due to time saved, but lack of technical expertise and internal resistance pose a significant hurdle to its acceptance.

Clinical data management involves collecting information in paper, electronic and digital formats across multiple trial locations from numerous sources that include clinical research organizations, laboratories, and investigative sites. *E-clinical* trials — the use of electronic data capture and Internet-based portals to collect and archive data for analysis — can streamline data collection and lead to more real-time reporting and faster analysis. By ultimately reducing the time taken to transfer the data from the patient to regulatory authorities, these trials improve productivity. However, less than 15% of clinical trial data are collected electronically because of resistance to change, lack of perceived net economic returns, and lack of standard formats.

1.2.4 Formulation and Drug Delivery

Many therapeutic agents have safety and efficacy shortcomings because of their inability to reach the target tissue, their non-selective targeting, drug instability in the body, or premature drug loss through rapid clearance and metabolism. There is a strong need in the cancer area for a delivery vehicle that

[53] The first companion test for Genentech's Herceptin™ was immunohistochemistry-based.
[54] SELDI-TOF-MS, for example, is very sensitive to every step in the analytical process, sequencing technologies need to drop dramatically in speed and price, or proteomic patterns lack discriminatory power (e.g., peaks may not necessarily originate from tumour-specific proteins).
[55] An example was the FDA's use of Pharsight's quantitative modelling and simulation software to help optimize the Phase II and Phase III clinical trial design for an anti-HIV drug.

selectively targets a cytotoxic drug to a tumour. The blood-brain barrier prevents the uptake of 98% of all potential neurotherapeutics and is a major factor in the failure of chemotherapies for brain tumours. National Research Council researchers have identified a novel class of antibody fragments termed nanobodies™,[56] which can cross the blood-brain barrier and have applications in diagnostics and CNS therapeutics.

Innovative delivery systems could also help salvage the 40% of active organic compounds coming out of the discovery pipeline that that may meet efficacy criteria but either are rejected because of solubility issues or require special formulation techniques to reach acceptable bioavailability. Decreasing particle size substantially increases surface area, thereby leading to an increase in dissolution. Approaches include sonochemical-assisted synthesis, supercritical fluid technology, and more recently high-gravity reactive precipitation, which reportedly can produce micro- and nanoparticles with a very narrow size distribution. Scale-up issues would have to be addressed, as promising solutions at the bench scale may not be successful in production. The Montreal subsidiary of UK-based SkyePharma develops and offers solubilization technologies to industry, both for clinical studies and post-marketing applications.

"Intelligent" implantable microchips being developed by Micralyne and others (e.g., with drug-filled reservoirs capped by gold foil that can be dissolved by an electrical charge, in response to chemical signals in the body) are under investigation as controlled-release agents to deliver drugs on demand. Applications include pain medications, anticancer agents, hormones, and steroids. Biodegradable branched polyesters consisting of poly (vinyl alcohol) (PVA) grafted with chains of poly (lactic-co-glycolic acid) (PLGA)[57] are another promising controlled-release strategy. By modifying the PVA backbone to create polymers with positive or negative charges or changing the length of the PLGA side chains, the vehicle can be adapted to carry small molecules, proteins, peptides or DNA. It can also be used in the mucosal delivery of vaccine-loaded nanoparticles with superior antigen capacity or in improved aerosol formulations for pulmonary drug delivery.

A drug of interest can be dissolved, entrapped, adsorbed, attached or encapsulated in a nano-based drug delivery vehicle, making it easier to penetrate blood vessels (particles smaller than 20 nm) and enter cells (less than 50 nm). Their small size enables superior targeting and accumulation at the target site. The high surface/volume ratio also allows for enhanced activity and solubility. Finally, sustained drug release at the target site can be achieved with the use of biodegradable materials. Major opportunities lie in cancer, central nervous system, respiratory, and cardiovascular diseases as well as vaccines and gene therapy.

Examples of nano-based delivery systems include:

- Polymeric micelles (spherical structures consisting of a hydrophobic core and hydrophilic shell). These are useful for the systemic delivery of water-insoluble drugs and targeted delivery of anticancer drugs because of their reduced propensity to accumulate in non-targeted areas. They are currently in clinical trials for the anticancer agents doxorubicin, cisplatin and taxol;

[56] This is a trade name owned by Belgium-based Ablynx. NRC is collaborating with Ablynx, which owns the dominant patent position in the field of nanobodies, initially for applications in Alzheimer's.

[57] Lea Ann Dailey et al, "The role of branched polyesters and their modifications in the development of modern drug delivery vehicles," Journal of Controlled Release (November 2004), p. 137.

- Polymeric biodegradable colloidal nanoparticles [e.g., poly-(butylcyanoacrylate) coated with polysorbate 80]. They have recently demonstrated feasibility in delivering drugs to the brain, and have potential applications in brain tumours and CNS disorders;
- Ceramic nanoparticles. Titanium dioxide nanoparticles can bind to DNA, sugars and peptides, opening up potential applications in gene therapy and antisense, as the attached oligonucleotide has been shown to cleave from the nanoparticle when illuminated. The design of an effective delivery method has been the greatest challenge in the development of RNA therapeutics, as the molecule must enter not only the tissue of interest but also the desired cells within the tissue;
- Quantum dots. These can be conjugated to DNA, proteins, or small molecule therapeutics; the attached protein or peptide could guide the particles to specific cells or to specific locations inside the cell where the attached drug would be released;
- Carbon nanotubes (sheets rolled up to form single or multiwalled tubes). These are potential carriers for plasmid DNA with applications in vaccines and gene therapy;
- Fullerenes. Buckeyballs have received considerable attention as drug delivery vehicles and as scaffolding for building drug molecules (chemical groups can be grafted to specific locations on the carbon-60 atoms). A major barrier to commercialization has been the cost of producing pure fullerenes in large quantities using the carbon arc method. A combustion synthesis process recently developed at MIT can tailor the product to a particular customer's requirements without the need for expensive post-solvent processing;
- Dendrimers (polymers characterized by a high degree of branching around a central backbone with extremely high surface multivalency or reaction sites, allowing coupling to multiple ligands). Their unique architecture makes them extremely versatile, with promising applications that include not only drug delivery (genes, vaccines, antivirals, antibacterials, and anticancer agents) but also photodynamic therapy (because of deeper tissue penetration), tissue engineering (by incorporating monomers such as glycerol or succinic acid), and magnetic resonance imaging. They can be used as well for controlled release (e.g., slow release of chemotherapeutics to minimize toxicity) or to transport extremely high densities of drug molecules. A recent development is boron neutron capture therapy (dendrimers containing boron atoms are conjugated to a monoclonal antibody, which targets a receptor in a tumour cell). Nevertheless, their biodistribution behaviour is still a major challenge as it is difficult to prepare dendritic polymers that circulate in the blood long enough to accumulate at target sites but are also eliminated rapidly enough to avoid toxicity. In addition, tissue localization is not easy to predict. Drug release studies associated with various dendritic architectures are also under investigation;
- Magnetic nanoparticles. Coated with biocompatible polymers and bound to drugs, these can be directed to particular sites in the body through the application of an external magnetic field.

Nanotechnology also has applications in clinical diagnostics. Ferumoxtran nanoparticles with an iron oxide crystal core coated with dextran are superior to gadolinium contrast agents for MRI. The particles remain in the body longer, so fewer doses are required; they provide a much clearer view of the margins of the tumour to help ensure it is completely removed; they highlight small tumours that gadolinium won't pick up, and enhance non-cancerous lesions caused by diseases such as Parkinson's.

In the vaccine arena, a variety of modified viral vectors including poxviruses (e.g., canarypox, novel adeno-associated viruses, and nonviral vectors such as plasmid DNA) are in development for experimental vaccines for AIDS, Ebola, human papillomavirus, rotavirus, and other infectious diseases. Adjuvants are another research area. The effectiveness of the immune response depends not only on the specific antigen but also on the adjuvant's general stimulation of the immune system. Adjuvants being tested with a potentially improved safety profile and/or enhanced immune stimulation over traditional aluminum salt derivatives include calcium phosphate nanoparticles, cytokines, CpG (nonmethylated cytidine-phosphate-guasosine) ologonucleotide sequences, and Toll-like receptor agonists. Because the immune response varies with the Toll-like receptor agonist used, it might be able to optimize protection to a given pathogen.[58]

Vaccines are usually administered by injection and many require a series of injections to be effective. Mucosal immunology is superior because most pathogens enter the body via mucosal surfaces, but with the exception of flu vaccines, commercial success has been difficult to achieve. Technical problems relate to antigen degradation, extensive dilution of the vaccine system, and immune reactivity to ingested or inhaled antigens. Nanoparticle carriers may overcome these challenges. Nanotechnology may also lead to the development of slow-release formulations that could reduce the need for boosters, a major advantage in countries where the health infrastructure is not well developed. The need for "cold chain" may be eliminated with a spray drying process based on anhydrobiosis, yielding vaccines that are stable to 55°C and preventing bacteria from spoiling the vaccine.[59] Whether the advantages outweigh the costs of clinical trials remains to be seen.

Topically applied vaccines using various adjuvants, transgenic edible plants that contain genes for human vaccine antigens, and controlled delivery depot systems with antigens encapsulated in biodegradable polymers are also under investigation. These delivery systems could reduce the need for refrigeration as well as the need for repeat injections. Although edible vaccines have potential benefits in terms of cost and the ability to initiate an immune response against intestinal bacteria, concern has been raised that they will deliver variable dose levels because fruits and vegetables are never of uniform size. This has led to a shift in strategy from food to capsules containing extracts, but it could be four years or more before such a product reaches clinical trials.

[58] A. Wack and R. Rappuoli, "Vaccinology at the beginning of the 21st century," Current Opinion in Immunology, Vol. 17 (2005), p. 414.

[59] Vaccine is spray-dried using a sugar syrup, which then hardens to form microscopic glass spheres that are then suspended in perfluorocarbon, an inert liquid. For combination vaccines, each component can be coated before being combined, ensuring they cannot interfere with each other, and the glass spheres can be made to dissolve at different rates, allowing booster doses to be given in the same injection as the initial vaccine.

1.3 Biomanufacturing

Biomanufacturing is defined here as the production of large molecules that cannot be directly synthesized or extracted. Relatively small, simple proteins are produced by microbial fermentation (e.g., insulin and human growth hormone in *E. coli*, recombinant hepatitis B vaccine in yeast). Larger, more complex proteins such as EPO, tPA, and monoclonal antibodies require the addition of specific sugar side chains to the protein backbone (a process termed glycosylation). Only mammalian cells — Chinese hamster ovary cell lines are the predominant industry standard — can naturally attach the right sequence of sugar molecules and fold the protein into its correct shape for it to be functionally active.

The commercial success of monoclonal antibodies, combined with the number of products in development, has raised concerns about the future availability of adequate cell-culture manufacturing capacity. However, cell densities and expression levels have increased dramatically over the past five years (e.g., from around 1 g/L up to a reported 5 g/L); targets of 10 g/L to 20 g/L by the end of the decade have been cited. This level will result from new, genetically engineered host vector systems, new media design, and nutrient feeding strategies based on knowledge of the metabolism of host cell strains. Examples include Crucell's human cell line PER.C6 expression system, which has been adapted to grow without components from serum or the need for microcarriers for cell attachment; the control of cell apoptosis by introducing an anti-apoptosis gene to ensure each cell functions longer, thereby increasing productivity; and high-throughput fluorescent-activated cell sorting techniques to identify the most productive cell lines.

Efforts are also underway to develop non-mammalian expression systems, such as GlycoFi's engineered Pichia pastoris yeast strains, which can produce glycosylated human proteins at a significant cost advantage. Non-glycosylated antibody formats utilizing antibody fragments such as Ablynx's nanobodies™ may also lower production costs, as these are capable of being manufactured in microbial cells.

Transgenic plants (as per Sembiosys, Calgary or Medicago, Quebec), the mammary glands or sperm of transgenic animals, and eggs from transgenic chickens may also offer attractive alternatives for the production of recombinant proteins. In contrast to plants, animal transformation processes are technically challenging and expensive: herds of animals require special care and take time to build up, and there is a risk that pathogens could be transmitted to humans, increasing handling and purification costs. The main technical issue regarding plants relates to glycosylation, as the protein may differ from the human counterpart. The cost advantage of plant transgenics over mammalian cell culture may not be fully realized if traditional cell culture manufacturing becomes more productive with more efficient cell lines. Further, the use of a protein expression system that requires weeks or months before a plant matures for harvest may be difficult to justify for cash-strapped companies that need to get their products through clinical trials as quickly as possible.

After the cell line, the culture medium and feeding strategies are the next most important factors that influence process performance. The development of first-generation serum-free media has led to present efforts to develop media that are chemically defined for superior consistency (e.g., replacing undefined components like plant protein hydrolysates with chemically defined peptide ingredients), which can reduce purification costs. The long-term strategy is to develop media that can quickly be individually optimized for a range of processes, but this is a challenge due to the diversity of cell lines and

production processes and the large number of media components. A shift in feeding strategies from batch operation towards fed-batch and perfusion could support high protein expression levels and yields and provide needed manufacturing capacity.[60]

As bioreactor efficiencies improve upstream, bottlenecks are moving downstream, leaving considerable room for improvement in product recovery and purification. Gains in these areas not only will reduce product costs but may permit an increase in capacity without requiring the building of an additional facility. Because the capacity of chromatographic and membrane materials to handle higher titre fermentation processes will be a challenge, new and refined chromatography methods are a major focus of attention. These include perfusion, expanded bed, adsorption, simulated moving bed and hydrophobic charge induction chromatography. New antibody purification materials with high selectivity and capacity are also required, such as mixed-membrane structures that combine affinity and separation.[61] Chromatographic surfaces on protein chips provide a novel tool for selecting the optimum resin based on predicted separation conditions and developing purification conditions. Multiple chromatographic functionalities and binding and wash conditions can be screened in parallel.[62]

1.4 Tissue Engineering

Tissue engineering is the regeneration of biological tissue by adding cells and biomolecules such as growth factors onto supporting highly porous structures or scaffolds to guide cell growth into a 3D structure. The scaffold that guides the shape of the new tissue may be either customized at the site of injury or produced *ex vivo* in a bioreactor and the resulting tissue construct reimplanted in the patient. It is a radically different approach than currently practised reconstructive medicine, which involves the placement of synthetic implantable devices to replace or augment diseased or damaged tissue; product performance is limited by the "unnatural" nature of the materials used. By regrowing new tissue structure and organs lost due to trauma or disease, tissue engineering offers a potential alternative to transplanted organs, which are in short supply and require lifetime treatment with costly immunosuppressive drugs.

The use of encapsulated islet cells to restore insulin function will be more effective in controlling glucose levels than insulin injections, while an artificial kidney incorporating human kidney epithelial cells will be less expensive than dialysis and a major improvement in quality of life. Active research areas include neural tissue, skin, bone, cartilage, liver, pancreas, heart valves, and myocardium. Although the use of stem cells to regenerate, for example, neurons in neurodegenerative diseases or beta cells in diabetic disorders would be a major therapeutic breakthrough, this will take many years. A shorter-term goal is to use stem cells to protect neuron cells or islet cells from dying in order to delay the severe consequences of late-stage disease.

[60] K. Carlson, "Flexibility—Guiding principle for antibody manufacturing," Nature Biotechnology (Sept. 2005), p. 1057.
[61] R. Werner, "The Development and Production of Biopharmaceuticals," Trends in Integrated Biomanufacturing, Special Supplement of BioProcess International (Sept. 2005), p. 11.
[62] See www.ciphergen.com for a description of this technology.

Tissue engineering is a multi-disciplinary field with research progressing on many fronts.

Biomaterials:

- scaffold materials that have the necessary surface properties to facilitate cell migration, adhesion and differentiation;
- materials tailored with biological ligands for the controlled release of growth factors or signalling molecules;
- nanotechnology to create material surfaces that can better guide the growth of seeded cells;
- fundamental understanding of the interaction of proteins with solid surfaces;
- understanding of the immune, inflammatory, and wound healing responses resulting from the scaffold materials;
- membrane selectivity and pore structure for bioartificial organs to protect transplanted cells;
- mathematical modelling of cells and their interactions in scaffold design;
- materials that can change their molecular conformation to external stimuli.

Cell types and their derivation:

- isolation and expansion of appropriate cell types;
- stem cell biology and factors affecting cell differentiation;
- culture conditions and biomarkers to optimize embryonic cell survival without promoting the growth of abnormal cells that could lead to cancer;
- differentiation of multiple cell types within a correct 3D framework;
- small molecules that can regulate stem cell differentiation and can be used as probes to verify that cells of the required type are produced;
- understanding of how cells interact with other tissue types;
- cell lines for creating specific tissues in tissue banks.

Biomechanics:

- identifying mechanical properties of normal tissue and the minimum properties required of engineered tissues;
- mechanical signals regulating engineered tissues;
- better mathematical models for musculoskeletal tissue engineering.

Biomolecules:

- growth factors to stimulate cellular function on scaffolds;
- vascularization of the cell transplant using controlled release of growth factors to induce angio genesis (or a novel polymer design with a vascular architecture).

Engineering design:

- bioreactor technology for producing commercial quantities of viable cells and for 3D tissue culture;
- techniques for the storage and preservation of cells and tissues;
- strategies to promote vascularization;
- *in vivo* sensors to monitor implanted organs for performance and to mimic the body's chemical sensing capability (lack of a reliable *in vivo* glucose sensor has been a major impediment to the development of an artificial pancreas).

Vascularization (formation of a network of blood vessels) of 3D soft organs is a major bottleneck if tissue engineering is to expand from relatively thin and simple structures such as skin or cartilage to more demanding applications such as blood vessels, skeletal muscles, and the heart. These must be fully integrated into the recipient's blood and nervous system to meet the implant's demands for oxygen and nutrients. In contrast to cartilage, for example, where only one cell type (chondrocytes) is needed for regeneration, a blood vessel consists of an inner layer of endothelium, a middle layer of smooth muscle cells, and an outer layer of connective tissue produced by fibroblasts. Integration requires considerable sophistication in scaffolding and simultaneous and/or sequential delivery of signals to three or more cell systems. Current vascularization strategies — addition of growth factors into the scaffold to induce angiogenesis after implantation or the pre-seeding of the implant with endothelial cells — may not be satisfactory because of a slow rate of vascular tissue remodelling and the complex nature of the highly branched microvascular networks necessary for maintaining viable cells. A novel alternative is organ printing: computer-assisted layer-by-layer jet-based deposition of cells into a 3D biodegradable gel with sequential maturation of the printed construct into vascularized tissue.[63]

Instead of using laboratory-grown tissues, which must be implanted, efforts are underway to develop methods that could deliver cells in a minimally invasive surgery format. For example, injectable systems in which cartilage cells could be added to a light-sensitive liquid polymer that hardens when exposed to ultraviolet light, encapsulating the cells, are in early-stage development.

Islet transplantation may be a potential cure for diabetes but there are problems with the availability of donor islets, as four donors per patient are often required, far more than in a whole-organ transplant. Investigators are working with fetal islet-cell clusters to identify islet stem cells and to expand islet numbers through *in vitro* cultivation before transplantation. Another approach is to identify the stem cell population in the adult pancreas and culture them to induce expansion.

The construction of a piece of a heart tissue has become one of the most urgent goals in tissue engineering. Scarred cardiac muscle caused by a heart attack increases strain on the surrounding healthy parts of the muscle, leading to further cell death, deformation of the cardiac wall, and eventual heart failure as the heart progressively loses its ability to pump enough blood to the body's organs. Unlike other tissues, the heart muscle (particularly its cardiomyocyte cells) has very limited, if any, capacity, for regeneration. Identifying different sources of stem cells [e.g., embryonic, fetal cardiomyocytes, skeletal myoblast (muscle cells), haematopoietic (bone marrow)] for transplantation to regrow necrotic scar tissue has been an active area of research. Challenges are numerous:

- the optimal quantity and timing of the dosage;
- the optimal delivery device;
- the long-term survival of the implanted cells, because the damaged area lacks the vital natural extracellular matrix that normally supports living cells;
- the failure of the cells to contract in synchrony with neighbouring cardiomyocytes, resulting in an electrical discontinuity across the heart wall that could trigger arrhythmias;
- alterations in the mechanical properties of the scar tissue; and
- determining whether transplanted myoblasts actually improve contractile function or just delay further deterioration.

[63] Vladimir Mironov et al, "Organ Printing: computer-aided jet based 3D tissue engineering," Trends in Biotechnology (April 2003).

An alternate strategy involves the development of small-molecule drugs that can coax cells that give rise to cardiomyocytes or stimulate bone marrow cells to migrate out of the bone marrow and implant inside damaged hearts. The LIFE (Living Implant from Engineering) initiative is an international endeavour created in 1998, spearheaded by the University of Toronto's Dr. Michael Sefton, to advance regenerative medicine as applied to the human heart.

Although there have been significant improvements in the design and performance of mechanical and tissue heart valves, they do not match that of normal valves. Mechanical valves, for example, suffer from thromboembolism, need for anticoagulation therapy, haemorrhage, and imperfect hemodynamic performance, while tissue valves have a durability problem, lack the capacity to grow, and have risk of endocarditis. Strategies for heart-valve tissue engineering include assembling biodegradable valve matrices made from synthetic material such as polyglycolic acid, biologic material such as collagen, or biologic material generated through nanotechnology, and populated by autologous or allogenic cells including stem cells that can express the necessary growth factors.

Only tissue-engineered skin and cartilage, and to a limited extent, bone, have reached the market, none of which can be classified as commercially successful. It will be at least 10 to 15 years before technical advances make a major impact in other areas. Without a dramatic decrease in manufacturing costs, the products are likely to be very expensive, so commercial success will hinge on the particular niche application and health care system acceptance of the higher costs. This will require strong economic data supporting the product's advantages over competing therapies and clear reimbursement guidelines. Reimbursement for the first tissue-engineered skin substitute, for example, was not available in the EU, while US Medicare guidelines restricted payment to one replacement graft and for only the most severe wounds. The protracted approval process for the pioneering tissue-engineered skin added substantially to their costs. Whether the establishment of the FDA Office of Combination Products in 2002 will reduce the regulatory burden on future products remains to be seen.

1.5 Benchmarking Canadian Biotechnology and Related Research: Discovery, Bibliometric and Patent Performance

The previous sections provided an overview of R&D trends in pharmaceutical biotechnology. The following discussion attempts to assess Canada's level of innovativeness by scanning scientific publications and patents to determine areas where Canada can compete globally to take advantage of these opportunities.

1.5.1 New Molecular Entities Discovered in Canada

According to an article in Nature Biotechnology,[64] the US accounted for 47% of new molecular entities and new biologics approved by the FDA between 1998 and 2003 (Japan was second at 10%), but this was in line with its share of the global pharmaceutical market. Canada ranked seventh, accounting for 2% (4 NMEs, 0 NBEs), but this was also equivalent to its global market share. A major Canadian weakness is the relative lack of activity in NBEs such as monoclonal antibodies which are the fastest growing segment of the biopharmaceutical market with diverse applications such as cancer, autoimmune, and

[64] R. Kneller, "National origin of new drugs," Letter to the Editor, Nature Biotechnology (June 2005), p. 655. The number differs from Figure 1 as it includes standard NMEs and NBEs.

inflammatory disorders. The UK and Switzerland scored comparatively higher than either the US or Canada because of the location of several large research organizations (e.g., Roche) in relation to their market size. Of particular interest is that 65% of all new drugs in the US and 50% in Canada were discovered in biotech companies, universities, or government laboratories, not in pharmaceutical companies. This contrasts with continental Europe and Japan.

1.5.2 Current Product Pipeline

Approximately 500 products are in various stages of development; however, close to two thirds of these are in the early research and preclinical stages. The most frequent indication is cancer, which accounted for about a third of activity, followed by infectious disease (15%) and neurological disorders (13%). These three together represented about 63% of all pipeline products. Table 3 below portrays development as of March 2005.

Table 3: Canadian Product Pipeline by Phase

	Research	Preclinical	Phase I	Phase II	Phase III	Submitted	Marketed
AIDS	3	5	2	1	1	1	0
Autoimmune	7	8	1	2	1	0	0
Blood Disorders	0	3	0	0	1	0	0
Cancer	63	54	17	30	11	5	1
Diabetes	9	6	2	1	0	0	1
Digestive Disorders	0	0	2	2	3	2	1
Eye	0	0	0	1	1	1	3
Growth Disorders	1	0	1	0	1	0	0
Heart Disease	25	7	5	3	7	1	0
Infectious Disease	20	35	4	9	6	3	2
Neurological	25	22	9	5	4	2	1
Respiratory	3	2	1	2	0	0	1
Skin Disorders	2	5	2	3	1	0	1
Stem Cells	2	0	0	0	0	0	0
Transplantation	2	1	0	2	0	0	0
Other	12	12	1	5	5	1	4
Total	**174**	**160**	**47**	**66**	**42**	**16**	**14**

Source: P. Winter, Biopharmaceutical Product Pipeline, Industry Canada internal study, March 2005.

1.5.3 Bibliometric Analysis

A summary of Canada's global share of science papers in selected fields and citation impact between 2000 and 2004 is provided below. The citation impact, a measure of how often an author's published work is cited, is particularly impressive in clinical medicine (38% above the world average), pharmacology (20%), and chemistry (18%), which suggests Canada is well positioned in the drug discovery and development phases.

Table 4: Percentage of Canadian Papers by Field and Citation Impact, 2000-2004

Field	Percentage	Citation Impact
Plant and Animal Sciences	6.39	+ 8
Neurosciences	6.33	+ 7
Molecular Biology & Genetics	5.36	+ 3
Computer Science	5.17	+ 8
Biology & Biochemistry	5.05	+ 4
Engineering	4.48	+ 5
Clinical Medicine	4.41	+38
Immunology	4.36	+ 4
Pharmacology	4.08	+20
Microbiology	4.10	+ 4
Chemistry	2.99	+18
Materials Science	2.99	+ 1

Source: Thomson Scientific, Science in Canada, April 2005, see http://in-cites.com/research/2005/april_4_2005-2.html

Biopharmaceutical Therapies and Technologies. Science-Metrix benchmarked Canada's position in therapies and technologies. Among therapies, the numbers of papers pertaining to diabetes, cholesterol, and psychiatric and neurological disorders rank higher than those referring to other research areas (Table 5).

Table 5: World Papers by Therapeutic Category, 1990-2001

	World	% Canada
Anti-arthritics	6,317	3.5
Anti-infectives	69,943	2.5
Antispasmodics	15,287	3.3
Antivirals	18,571	2.4
Bronchial & Other Respiratory	48,555	3.8
Cancer	91,341	2.8
Cardiovascular	91,749	3.9
Cholesterol	14,304	4.1
Contraceptives	3,293	2.4
Dermatology	23,529	2.5
Diabetes	30,732	4.4
Hemostatic Modifiers	42,820	3.5
Hormones	43,374	3.9
Psychotherapies & CNS Disorders	105,096	4.0
Vaccines & Immunotherapies	42,905	2.6
Total World	**747,816**	**3.6**

Source: Science-Metrix, Biopharmaceutics in Canada, Benchmarking of Canadian Biopharmaceutical Science and Technology, May 2003.

If publications are sorted by technology, the emphasis is on bioinformatics, nanotechnology, and genomics (Table 6). When technologies and therapies are considered in pairs, the use of regenerative medicine in cardiovascular disease and the application of genomics in diabetes research are areas where Canada has the strongest impact on the world scientific community. The application of antibodies and imaging technologies in the treatment of cancer also has a relatively high impact, but this does not apply to nanotechnology in cancer, where Canada is relatively weak.

Table 6: World Papers in Biopharmaceuticals by Technology, 1990-2001

	World	% Canada
Antibodies	56,985	3.2
Bioinformatics	3,227	3.9
Combinatorial Chemistry/Screening	6,638	3.3
Genomics/Proteomics	146,507	3.8
Imaging/Biophotonics	63,104	3.6
Mass Spectrometry	2,284	3.5
Mimetics	14,318	3.4
Nanotechnology	31,538	3.9
Regenerative Medicine	27,648	3.2
Total World	**352,249**	**3.6**

Source: Science-Metrix, Biopharmaceutics in Canada, Benchmarking of Canadian Biopharmaceutical Science and Technology, May 2003.

Pharmacogenomics.[65] There is an increasing gap between Canadian and global scientific output in pharmacogenomics. At the world level, the number of research papers grew from 273 in 1991 to 1,671 in 2002, while Canadian growth, from 17 to 57, was less significant. In addition, Canada has few industrial players with major research efforts in this area.

Another survey[66] found 1,828 papers were published on single nucleotide polymorphisms (SNPs) between 1987 and 2001, with 82% between 1998 and 2001, indicating the field is relatively young. The majority came from public research institutions in the US and Japan, and the top cited authors are US and Scandinavian based. In Canada, the greatest number of papers originated from McGill University. As can be expected, few biotechnology companies published research papers. Of the top 10 that did, nine are based in the US.

Stem Cells. The global output in papers related to stem cell research has increased from around 3,000 in 1994 to 7,000 in 2003. Publication output and citation share for selected countries are shown in Table 7. The US contributes about 46% of all publications to the world total but attracts about 65% of all citations. Canada has a relatively high citation impact for its share of papers. The University of Toronto is the only Canadian institution in the top 20 most active institutions, with a 1.31% share of papers and a 2.56% share of citations (the leader is Harvard, with 4.81% and 7.78% respectively). It

[65] Ibid.
[66] Roger Coronini et al, "Decoding the literature on genetic variation: survey of the scientific and patent literature on single nucleotide variants," Nature Biotechnology (January 2003), pp. 21-29.

should be noted that Canada's share of world papers decreased from 4.8% during the period 1994-1997 to 4.4% from 2000 to 2003, largely because of growth in the number of research papers from other nations. Because the acquisition, characterization, differentiation, and growth of cells is central to the whole process of tissue engineering, research funding will have to be increased if Canada is to have a major stake in regenerative medicine.

Table 7: Stem Cell Research — Publication Output and Citations for Selected Countries, 1994-2003

	No. Publications	Percentage	Citation Share (%)
US	21,780	46.4	65.0
Japan	5,468	11.6	9.2
Germany	4,750	10.0	8.3
UK	3,995	8.5	8.0
France	3,324	7.0	6.5
Italy	2,611	5.6	3.3
Canada	2,201	4.7	6.4
Total World	**46,964**		

Source: W. Glanzel, "Stem Cells: An Analysis of an Emerging Domain of Scientific and Technological Endeavour," Final Report, Steunpunt O&O Statistieken, December 2004.

1.5.4 Patent Performance

Patents obtained are another indicator of scientific and technological presence. Table 8 presents biotechnology patent activity at both the US Patent and Trademark Office (USPTO) and the European Patent Office (EPO) for 1992-2001. As shown, Canada ranked sixth in the number of biotechnology patents granted at the USPTO and eighth at the EPO, below its rank in number of companies. Biotechnology patents are divided into a number of fields, so it is not possible to determine from the above data a country's position in a particular biopharmaceutical technology.

Table 8: Select Countries with more than 200 Biotech Patents at the USPTO and EPO, 1992-2001

	USPTO		EPO	
	Patents	Share(%)	Patents	Share(%)
US	31,570	61.1	18,776	42.2
Japan	4,159	8.1	4,361	9.8
Germany	2,590	5.0	4,340	9.8
UK	2,297	4.5	3,338	7.5
France	1,715	3.3	2,429	5.5
Canada	1,666	3.2	1,193	2.7
Netherlands	965	1.9	1,426	3.2
Switzerland	913	1.8	1,364	3.1
Denmark	742	1.4	863	1.9
Australia	612	1.2	695	1.6
Sweden	583	1.1	799	1.8
Italy	575	1.1	789	1.8
Israel	448	0.9	496	1.1

Source: W. Glanzel et al, Domain Study: Biotechnology—An Analysis based on Publications and Patents, Steunpunt O&O Statistieken, November 2003.

While patenting is a broad indicator of technological activity, patent citations provide a measure of the importance of the underlying invention — widely cited patents tend to be seminal patents. An analysis by Science-Metrix[67] of biopharmaceutical patents from 1990 to 2001 showed that while Canada ranked fifth in terms of number of patents at the world level, its ranking in average citations per patent was eighth and below the world average in terms of citations per patent. Canadian patents may have been on average relatively less important than its major competitors, or there may have been comparatively little activity in technologies such as genomics, combinatorial chemistry, antisense, therapeutic monoclonal antibodies, and gene therapy.

Pharmacogenomics. From 1987 to 2001, 365 patents or patent applications were filed on the topic of SNPs.[68] Approximately 76% were from research-based biotechnology companies with the remaining held by supplier companies, big pharma, and not-for-profit research centres. US firms dominate the field, developing SNP technology platforms into drug discovery programs, genotyping services, or diagnostic kits.

Molecular Farming. Major enabling technologies used in plant biotechnology are owned by multinationals. These include transformation methods (means by which foreign DNA is inserted into the host cells, the most popular being agrobacterium-based systems and the use of microprojectiles to physically project tiny particles coated in DNA through plant cell walls); use of selectable markers to identify the transformants; and expression methods (mechanisms to control the activity of the recombinant genes

[67] Biopharmaceuticals in Canada—Benchmarking of Canadian Biopharmaceutical Science and Technology, report prepared for Industry Canada (March 2003).
[68] Roger Coronini et al, "Decoding the literature on genetic variation: survey of the scientific and patent literature on single nucleotide variants," Nature Biotechnology (January 2003), pp. 21-29.

and the recovery of the recombinant gene products). The larger companies are able to get around broad claims of these early patents through cross licensing, which is a strategy not readily available to smaller firms. Patents specific to molecular farming include plant or animal transformation methods, plant-specific applications, and artificial chromosomes. Canada's position is shown in Table 9. Several Canadian firms have recently vacated the animal molecular farming field, leaving Canada without a major player with respect to production of biopharmaceuticals.

Table 9: Major Issued and Applied Molecular Farming Patents, 1991-2003

	Animal	Plant
US	254	104
Canada	61	15
Germany	31	3
France	12	3
Netherlands	11	-
Japan	11	2
UK	10	27
Switzerland	7	-
Israel	7	-
Belgium	5	14

Source: F. Arcand, and P. Arnison, Development of Novel Protein Production Systems and Economic Opportunities & Regulatory Challenges for Canada, Industry Canada internal report, April 2004.

Stem Cells. Patents may involve the cells themselves (newly isolated stem cells, undifferentiated stem cell lines, differentiated stem cell lines or genetically modified stem cell lines); processes involved in their isolation, modification, or proliferation; or applications for any of these, including research/diagnostic tools, therapies for the treatment of certain medical conditions, and cloning of organisms.

Table 10: Stem Cell Patents for Selected Countries, 1994-2003

	USPTO (granted)	EPO (applications)
US	672 (74%)	472 (53.4%)
Canada	41 (4.5%)	32 (3.6%)
Japan	37 (4.1%)	76 (8.6%)
Germany	29 (3.2%)	56 (6.3%)
France	25 (2.8%)	39 (4.4%)
UK	19 (2.1%)	36 (4.1%)
Israel	18 (2.0%)	24 (2.7%)
Total World	**904 (100%)**	**863 (100%)**

Source: W. Glanzel, "Stem Cells: An Analysis of an Emerging Domain of Scientific and Technological Endeavour," Final Report, Steunpunt O&O Statistieken, Dec. 2004.

In the field of isolated embryonic stem cells, the leading breakthroughs came from scientists at the University of Wisconsin, Johns Hopkins, and the University of Edinburgh. Each of these institutions has entered into collaborative relationships with US-based Geron Corporation. Geron, for example, has a worldwide exclusive licence from the Wisconsin Alumni Research Foundation (WARF) to develop therapeutic and diagnostic products from neural cells, cardiomyocytes, and pancreatic islet cells, and non-exclusive rights to products from hematopoietic, chondrocyte, and ostoeblast cells. WARF has a broad US patent on a method for deriving human embryonic stem cells and on the cells themselves, but its EPO application was declined in 2004 on the grounds that it was contrary to "public morality" because the method would require the use of a human embryo as a starting material. Companies working with adult-derived stem cells are out of reach of WARF's patents. While governmental, academic and non-profit researchers have access to the patented stem cell materials without royalties or fees, this is not the case with companies — Canadian or otherwise — who will have to negotiate licence agreements from Geron or current patent holders.

Nanotechnology. The USPTO issued approximately 22,600 nanotechnology patents from January 2000 to April 2003, with the US accounting for 79%; the top ten filers included Japan, France, UK, Taiwan, Korea, Netherlands, Switzerland, Italy, and Australia. The fastest growth, an indication of potential future development trends, has been in the chemical and pharmaceutical fields, followed by semiconductor devices. The most important topics were nucleic acids, pharmaceutical compositions, coating compositions, laser beams, and optical systems.[69] The life science companies that own the greatest number of US nanotechnology patents are Abbott Laboratories, Eli Lilly, Genentech, Merck, and SmithKline Beecham.

1.5.5 Technology Expertise Consultation Findings

Senior managers and researchers from Canadian industry, government and universities at the Bio-Pharma Technology Roadmap Focus Days were asked to list the 15 most promising technologies for the biopharmaceutical industry and to rank them in terms of Canada's perceived strengths compared globally (Table 11).

[69] Huang, Zan et al, "Longitudinal Patent Analysis for Nanoscale Science and Engineering: Country, Institution, and Technology Field," Journal of Nanoparticle Research (2003), Vol. 5, Issue 3-4, p. 45.

Table 11: TRM Stakeholders' List of Important Technologies

Technology	Description
Genomics	Includes gene chips, micro arrays, expression analysis
Proteomics	Studies of protein identity, interactions, 2D gels
Bioinformatics	Gene and database mining, DNA profiling
Metabolomics	Metabolic profiling, drug effects
Pharmacogenomics	Individual response to drugs and disease, personalized medicines or treatment
In silico Biology	Modelling of drug effects and interactions
Nanotechnologies	Miniaturized or molecule-sized technologies
Stem Cell Technologies	Tissue- and cell-based regeneration
Photodynamic Technologies	Light-activated processes
Combinatorial Chemistry	Small molecule new drug libraries; rational drug design
High-throughput Screening	Technologies for candidate assessment and drug or lead discovery
Monoclonal Antibodies	Human antibodies, vaccines, products
Manufacturing Technologies	Protein production, fermentation, cell culture, molecular farming or access to GMP facilities
Drug Delivery Technologies	New methods for drug delivery
Biosensors	Bio-based sensing of drugs, effects, efficacy

Source: TRM Steering Committee.

Their identification of the important technologies is similar to that reported in other reviews. Most felt that Canada had niche strengths in genomics, proteomics, photodynamic therapy, clinical trials, stem cell and regenerative medicine, biochips and biosensors.

1.6 Canada's Biotechnology Funding Strategy

1.6.1 Overall Canadian R&D Funding and International Comparisons

Some annual statistics on government expenditures are available specifically for the biotechnology sector. Additional insight can be obtained by reviewing data on total science and technology expenditures and outcomes in Canada and comparing them to health and biotechnology expenditures. A recent study by the Advisory Council on Science and Technology[70] also assessed government, business and higher education R&D expenses and performance. The data are quite informative.

In 2005, of the total gross expenditures on R&D (GERD) of $26.3B (1.96% of GDP), 47% of funds were sourced from business, 19% from the federal government, 6% from provinces, 16% from universities, 8% from foreign sources and 3% from private and non-profit groups. The GERD has increased from about $11.5B in 1993. Expenditures by universities, business and foreign sources have

[70] C. Riddle, Taking Stock of R&D across Three Sectors, ACST Preliminary Report (June 2003).

increased more rapidly than government R&D, driven by government policy, federal funding and a rapidly growing economy. As a result, the proportion of R&D performed by the government has declined from 30% in the 1970s to current levels.[71]

Table 12: Canada's R&D Expenditures by Source of Funds and Performing Sector, 2005 (C$B)

Funder	Total	Percent by Funder	Performer	Percent by Performer
Total	26.30	100	26.80	100.0
Federal Government	5.00	19	2.10	8.0
Provincial Government	1.70	6	.37	1.4
Business Enterprises	12.40	47	13.80	51.5
Higher Education	4.30	16	9.80	37.0
Private Non-profit	.76	3	.74	3.0
Percent by Source	100	---	100	---

Source: Statistics Canada, Estimates of Gross Expenditures on Research and Development (GERD), Canada, 1992 to 2005, Cat. No. 88-0006-XIE, Vol. 29 No. 2, December 2005.

Business funding of R&D can be seen as a driving force of change in the overall GERD/GDP ratios, since it is the dominant funding source in countries having a high level of R&D. However, compared with other OECD countries, the proportion of business financing of R&D in the higher education sector is high in Canada among G7 countries and has been increasing. In Canada, approximately 5% of industrial R&D is subcontracted to universities, as compared with 1.5% in the US. Similarly, Canadian university R&D receives about 12% of its budget from industry, as compared with 5% in the US.[72]

When Canada's share of national income allocated to R&D and new knowledge creation is compared with OECD countries, Canada is seventh, behind Sweden, the US, Finland, Korea, Denmark and Japan and behind the EU average. Business funding of R&D in Canada at 47% dramatically trails BERD in Japan (75%) the US (63%) and the OECD average (62%). In contrast, higher education R&D spending (HERD) as a percentage of GDP in Canada (16%) ranks fifth and as a performer (37%) ranks highest in the OECD.

Summarizing the data and comparing with the US, EU and OECD, the following can be concluded (Table 12) about Canada:

- The amount of R&D performed by the government is higher than the US and close to the OECD average (11%);
- The amount of R&D financed by government is near that of all other jurisdictions;
- The amount of R&D performed by the higher education sector is among the highest of all comparison regions and double the OECD average;

[71] Statistics Canada, Total Spending on Research and Development in Canada 1990-2005, Catalogue 88-001-XIE, Vol. 29, No. 8 (December 2005).
[72] OECD Science, Technology, and Industry Scoreboard 2005. http://miranda.sourceoecd.org/vl=3277118/cl=29/nw=1/rpsv/scoreboard/

- Industry is the dominant source of R&D funds;
- The amount of R&D performed by business was lowest for Canada (59% in 2003), 88% of the OECD average and 85% of that in the US.

Table 13: Comparison of GERD 2003 for Canada, US, the EU and the OECD

	Canada	US	EU-15	Japan	OECD
R&D/GDP (%)	1.9	2.6	2.0	3.2	2.2
R&D by Performing Sector*					
• Industry	53	69	64	75	67
• Government	11	9	13	9	11
• Higher education	36	17	22	14	19
• Private/non-profit	-	5	1	2	3

Source: OECD Science, Technology, and Industry Scoreboard 2005. http://miranda.sourceoecd.org/vl=3277118/cl=29/nw=1/rpsv/scoreboard/. The latest year available for comparative data is 2003.
**Note that the sector data are percentages of GERD.*

This means that Canada relies on universities to perform research and innovation twice as much as the US (at 17%) and much more than the EU (at 22%). In addition, Canada relies on industry for development at a level of only 79% of the OECD 2003 average. This suggests that business, which is expected to be financing and performing development (as opposed to research and discovery) may be under-investing in this activity. The question is whether this is due to lack of funds or lack of strong opportunities for investment.

1.6.2 Funding of R&D in the Health Field

Statistics Canada has recently compiled R&D expenditures in the health field,[73] some of which are relevant to this analysis.

- Total R&D expenditures in the health field in 2004 amounted to about $5.7B, or about 23% of all R&D expenditures.
- The higher education sector performs 58.6% of health-related R&D, compared with 35% for the total science sector; business undertakes 35%, compared with 54% for total science R&D; and government accounts for 4%, compared with 10% for total R&D.
- Government funds 17% of R&D in the health field, compared with 19% for the total science sector; business funds 30%, compared with 44% of the total; higher education funds 25%, compared with 16%; and foreign sources fund 14%, compared with 12% of total R&D.

Clearly, Canada relies especially heavily on university research in the health field. This reliance indicates that the bulk of funding for R&D emphasizes the R side and less of the D or product development side. These trends are accentuated in biotechnology funding.

[73] Statistics Canada, Estimates of Total Expenditures on Research and Development in the Health Field in Canada, 1988 to 2004, 88-001-XIE, Vol. 29, No. 5 (July 2005).

Table 14: Gross Domestic Expenditures on Health R&D by Performing Sector

Year	Govts	Businesses	Higher Education	Other	Total	Health R&D/GERD
2000	158	1,255	2,104	44	3,561	17.3
2001	194	1,517	2,383	40	4,956	18.2
2002	228	1,758	2,930	40	4,956	22.2
2003	249	1,896	3,095	41	5,281	22.7
2004	237	2,002	3,367	42	5,748	23.5

Source: Statistics Canada, Estimates of Total Expenditures on Research and Development in the Health Field in Canada 1988 to 2004, 88-001-XIE, Vol. 29, No. 5, July 2005, Table 2 and Chart 3.

1.6.3 Government Biotechnology Strategy and Funding

Total financing of R&D and related science activities in all branches of biotechnology (including agri-bio and biopharmaceuticals) doubled from $319.5M in 1998-1999 to $746M in 2003-2004.[74] Recognizing the importance of a strong biotechnology research base, the federal government decided in the mid-1990s and subsequent years to empower fundamental scientific research in Canada, including the fields of genomics and biopharmaceuticals.[75] One goal of this approach is to establish a critical mass of research infrastructure, including large pools of post-graduate and post-doctoral researchers and internationally renowned principal investigators.

In Canada, the provincial and federal governments jointly support academic research. The provinces provide the basic physical infrastructure and operating costs. The federal government funds the direct costs of research, mainly through the three national research granting agencies: The Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC). In addition to the support delivered at the federal level are provincial research programs; in particular, provincially funded cancer institutes.

These ongoing programs are now supplemented by a variety of programs to reinforce the research and discovery base, including research in the new biotechnologies taking place in universities and hospitals. The main vehicles for delivering government support include Genome Canada, the Networks of Centres of Excellence (NCEs), the National Research Council (NRC) the Industrial Research Assistance Program (IRAP) of the NRC, the Canada Foundation for Innovation (CFI), Technology Partnerships Canada (TPC) or its successor, if any, R&D tax credits (SR&EDs), and the Canada Research Chairs Program. The contributions to encourage commercialization — TPC, IRAP and Canada's R&D tax credit program—are overseen by Industry Canada and administered by the relevant funding agencies and the Canada Revenue Agency.

In 2004-2005, levels of funding for biopharmaceutical R&D and related scientific activities by federal labs and granting councils amounted to approximately $610M. Higher education continued to be the

[74] Statistics Canada, Biotechnology Scientific Activities in Federal Government Departments and Agencies, 2004-2005, 88-001-XIE, Vol. 30, No. 2 (March 2006), Table 2 and Table 3A.

[75] The new funding followed on reports by national advisory committees about the current status and potential of the industry, e.g., Leading in the New Millennium, (1998) Sixth Report of the National Biotechnology Advisory Committee.

largest recipient, receiving nearly $400 million, an increase of about 6% over the 2003-2004 expenditures. The amounts can be broken down as follows.[76]

Canadian Institutes of Health Research. $299.2M for biotechnology. CIHR is a major funding organization with an annual budget of $560M that currently funds over 5,000 researchers in universities, research institutes and training hospitals across Canada. CIHR also offers partnership programs with small and medium-sized enterprises and research-based pharmaceutical companies that emphasize the pipeline between the lab bench and the marketplace, aiming to strengthen Canada's technology transfer and commercialization processes.

National Research Council. $134.3M directed to biotechnology. Canada's foremost enabler and facilitator of advanced scientific research (annual budget of $900M), NRC is a strong supporter of biopharmaceutical research through:

- the Biotechnology Research Institute in Montreal;
- the Institute of Biodiagnostics in Winnipeg;
- the Institute of Biological Sciences in Ottawa;
- the Institute for Nutrisciences and Health in Charlottetown.

Genome Canada. $82.7M for biotechnology R&D and related scientific activity. Genome Canada is the hub of a national network of researchers in genomics and proteomics with five Genome Centres across the country. In fact, the centres also research applications in agriculture, environment, fisheries and forestry in addition to health and new technology and leverage the GC money through domestic and international partnerships.

The Canada Foundation for Innovation. $71 M spending on biotechnology R&D and related scientific activity. CFI was created with a budget of $3.15B to strengthen R&D infrastructure by providing 40% of a project's cost in Canadian universities and hospitals, through investments in building and equipment. Investments in genomics, proteomics, bioinformatics and nanotechnology total about 60% of the innovation fund.

The Natural Sciences and Engineering Research Council. $63.1M in 2004-2005 support for biotechnology R&D. NSERC is a major program that promotes innovation and discovery through funding more than 9,000 university-based investigators every year, as well as annually offering scholarships and fellowships to Canada's brightest advanced students. Major biotechnology commitments include biotechnology institutes in Saskatoon, Ottawa, Montreal, St. John's, Halifax, and PEI.

The National Centres of Excellence.[77] A research support organization, NCE's mission is to create networks and critical mass in selected areas of strategic importance to Canada. The program has an annual budget of $77.4M, which it leverages through links with federal and provincial government departments, industry and universities, so that the total support it offers to researchers is $149M. Of the 19 NCEs currently receiving funds from the program, four are working in areas with a biopharmaceutical dimension, including:

[76] Ibid. See also Kathryn Howard, Director General, Life Sciences Branch, Industry Canada, Presentation to BioteCanada Conference 2003: Adapting to the Times (29 May, 2003), slides 3-7.
[77] NCE Annual Report 2004-2005, available at: www.nce.gc.ca/annualreport2004_2005/Eng/2_3/2_3_3.asp#2_5_6

- Allergy, Genes and Environment Network - AllerGen (2004-2009)
- Canadian Arthritis Network - CAN (1998-2009)
- Canadian Genetic Diseases Network - CGDN (1989-2007)
- Canadian Network for Vaccines and Immunotherapeutics - CANVAC (1999-2006)

The Canada Research Chairs Program. A major effort by the Government of Canada to strengthen university research has involved spending $900M to fund 2,000 Canada Research Chairs at universities across the country. Of these, only a portion is in the life sciences (microbiology, biochemistry and life sciences related to human health and disease).[78]

Indirect Costs. The federal government has indicated in recent budgets, from 2003 to date, that it will invest $190M to cover indirect costs of research related to operating infrastructure in addition to the direct costs of research. Provincial governments provide the basic infrastructure. Examples of provincial government programs that support biopharmaceutical research (including genomics and proteomics) include the Ministère du Développement économique, de l'Innovation et de l'Exportation, Québec, and the Ontario Research and Development Challenge Fund.

1.7 Recommendations for Strengthening Biotechnology Scientific Results

Drug discovery and development is becoming more and more challenging and expensive, as evidenced by the decline in approvals and increase in late-stage and post-marketing failures. Rising costs have also engendered concern about the affordability of future therapies. Failures are the result of poor target selection, the inability to find a druggable target, lack of progression beyond the preclinical or early clinical stages because of poor ADMET properties, poor or non-responsiveness during clinical trials, or safety issues that arise after approval.

Consequently, tools that can improve target identification and validation, predict compound toxicity earlier, and identify patient responders are of utmost priority. There is a need for better predictive models of disease and an increased role for computer modelling and simulation. Technologies that can improve the discovery and development process include stem cells and systems biology for target identification; RNA interference, metabolomics and chemical genomics for target validation; high-content screening and *in silico* modelling technologies to guide lead selection and optimization as well as ADMET prediction; human microdosing safety studies; clinical trial modelling and simulation; and new biomarkers as substitutes of clinical response in areas such as neurodegeneration, psychiatry, and oncology.

Scientific challenges are in fact opportunities, and the following recommendations are directed towards government financing, urging first, that more resources be devoted to building development capacity for biologics and in particular, that targeted support be directed towards:

[78] Industry Canada; 14 chairs are Tier One ($1.4M over 7 years) and 16 are Tier Two ($0.5M over 5 years).

- increased investment in computational chemistry and molecular modelling;
- drug target validation platforms, one of the most important areas in discovery research;
- operating funding for screening and other core discovery facilities in academic institutions;
- increased funding for new technologies to predict preclinical/clinical safety and for enhanced education and training within academia, with additional support collaborations between academia, industry and regulatory authorities;
- research programs in systems biology and chemical biology;
- increased emphasis in universities and funding programs on glycobiology;
- increased support to ensure the necessary human resources are available as the industry develops, including:
  - Increasing number of products entering the clinic will lead to an increased demand for multidisciplinary clinical researchers with expertise in tools such as proteomics, imaging, and bioinformatics, and, particularly, expertise in safety assessment of new medicines.
  - Support initiatives that encourage technology convergence and cross training opportunities in regenerative medicine with other disciplines.

Finally, formulation development and drug delivery are important to product success, yet Canada's research capabilities are not well developed and it is proving difficult to attract, develop and retain the necessary expertise.

In addition, support for the following areas would enhance Canada's capacity for leadership:

- Early-stage funding is needed for synthetic biology — entry costs are relatively low and there are currently no global leaders, so more funding would open an opportunity for Canada;
- A national nano-biotechnology research strategy, especially in health applications, should be developed to promote convergence of nanotechnology with life sciences. Levels of government support must be increased to be competitive with other major countries. The strategy should foster interdisciplinary training opportunities with other disciplines such as polymer chemistry, colloidal science, biophysics, molecular biology, surface chemistry, and engineering, and additional support should be available for biofabrication techniques;
- High-performance computing has made a major impact on drug discovery, from the Human Genome Project to *in silico* research, but Canada is lagging. Extra computing power will be required to handle the complex calculations of protein-folding reactions or to accurately model the behaviour of a cell. Few life science firms can afford a supercomputer and many universities and government research laboratories around the world are turning to grid computing, using the Internet to increase server utilization and computing power to handle the complex data being generated in scientific research. In Canada, grid computing is still in its infancy.

Part 2
Commercialization Challenges

2.1 From Lab Bench to Clinical Practice: Commercialization is Canada's Best Opportunity but Weakest Link!

Canada, like every other industrial economy, relies on the commercialization process to move discoveries from the lab bench to clinical practice. Upon the success of that process also depends the realization of value from the substantial investments in discovery research. That value includes new knowledge, techniques and expertise in health care delivery, the dramatic therapeutic benefit of new products, as well as associated jobs, exports and tax revenue. Commercialization is likewise the foundation of a robust industry sector able to create substantial value and drive prosperity in a knowledge-based global economy. This section examines Canada's strengths, the hurdles facing Canadian companies due to the challenges posed by the new technologies, and the current status of the industry. A discussion of the growing demand for new therapies sets the scene.

2.2 Therapeutic Market Opportunities

According to the US Centers for Disease Control and Prevention, the five leading causes of death in the US (excluding accidents) are cardiovascular disease, cancers of various types, cerebrovascular disease, chronic lower respiratory disorders, and diabetes. Many of these conditions are strongly age-related as are illnesses such as arthritis, Alzheimer's, and Parkinson's that reduce an individual's quality of life.

2.2.1 Cardiovascular Disease

Hypertension and hyperlipidaemia, the two largest segments, are relatively well served, although there is a lack of promising targets for hypertension. They are also expensive markets to enter because of the sales and marketing resources required and the need for very large clinical trials to demonstrate clinical superiority. The largest unmet need exists in markets with relatively small populations such as congestive heart failure. Over 500,000 new cases are diagnosed in North America each year and it is the single most common reason for hospitalizations of persons over 65, involving about one million admissions. It is a progressive disease with poor prognosis — approximately 30% with new onset heart failure die within one year of diagnosis. Most new and emerging therapies represent nearly equivalent substitutes for older drugs rather than new concepts for treating the disease.

2.2.2 Cancer

Cancer, the second leading cause of death after heart disease, is expected to take the lives of about 600,000 North Americans, with lung cancer accounting for 28% of mortalities, followed by colorectal, breast, pancreatic, and prostate cancers. Poorly served by traditional chemotherapies, cancer is a major opportunity for biotech firms. The investment needed is lower than other diseases because the field has high priority with regulatory authorities, who are willing to give it fast-track status based on smaller (and therefore cheaper) clinical trials (a few extra months of survival may be enough to win FDA approval). The clinical community is highly concentrated; and the market size is often larger than the approved indication because of high off-label use. However, virtually all cancer drugs face a major hurdle in establishing efficacy in late-stage disease. It is also unlikely that any newly developed therapeutic will be successful independently; it will probably be used in combination with existing drugs.

The most notable trend in cancer research is the push to targeted therapies. Examples include the HER2 molecule over-expressed in certain breast tumours, CD20 molecules on lymphoid cells, and the

epidermal growth factor receptor, which is over-expressed in a variety of solid tumours. Also under development are more targeted chemotherapeutics using novel drug delivery systems. Because targeted therapies will only be applicable to certain segments of the patient population or certain forms of the disease, the FDA may require that pharmacogenomic biomarkers be available to determine whether the patient is likely to respond to the therapy.

2.2.3 Central Nervous System Disorders

Central nervous system disorders (CNS) disorders include a broad variety of complications — from the acute neurodegeneration that comes in the wake of a catastrophic event (stroke, spinal cord injury, traumatic brain injury) through acute and chronic pain; motor neuron diseases such as amyotrophic lateral sclerosis; epilepsy; autism and learning disabilities such as attention deficit hyperactivity disorder (ADHD); drug addiction; multiple sclerosis; and psychiatric diseases such as schizophrenia, depression and anxiety to the slow, progressive loss of nerve cells that leads to conditions such as Alzheimer's and Parkinson's diseases. Among acute CNS disorders, stroke is by far the most prevalent. It is the third leading cause of death, and the leading cause of long-term disability. Of the almost half a million individuals who annually suffer strokes, about one third die and one third are permanently disabled.

Global sales for CNS drugs are estimated at around US$65 billion; it is the fastest growing segment of the pharmaceutical market. Nevertheless, treatments for most disorders are either suboptimal or not available. For example, tissue plasminogen activator (tPA), the only approved drug for the treatment of ischemic stroke, has not been accepted by many emergency physicians because of its narrow window of opportunity (it must be administered within three hours of a stroke's onset), increased risk of intracerebral haemorrhage, and modest efficacy. There is a need for therapies that can significantly reduce side effects associated with existing drugs, delay progression of neurodegenerative diseases such as Alzheimer's, penetrate the blood-brain barrier for superior efficacy, or provide much more rapid onset of action (e.g., antidepressants).

The greatest growth potential in the near to medium term is in therapies for pain (e.g., lower back pain, osteoarthritis, neuropathic pain, US population approximately 60M), addiction (smoking, drugs of abuse, US population approximately 50M), Alzheimer's, and Parkinson's). Four million North Americans are affected by Alzheimer's disease; this is likely to increase to 14 million by the middle of this century. Incidence rises steeply with age and may be as high as 20% in people over 80. Delaying progression by five years would lead to a 50% decline in AD patients; delaying it by 10 years would virtually wipe out the disease, as older people would die of other disorders. Parkinson's affects approximately one million individuals; there are few key players and few new drugs.

2.2.4 Musculoskeletal Disorders

These disorders cause serious pain and contribute to major losses in mobility and independence. Osteoporosis is responsible for hip and wrist fractures, spinal deformity and vertebral fractures, particularly in post-menopausal women. Osteoarthritis causes degeneration of the articular surfaces of the hips, knees, and spine. Problems with boney and soft tissues of the feet are common causes of pain, immobility and chronic wounds. More than 35 million women are affected by osteoporosis in the G-7 countries, while a similar number of men and women are affected by osteoarthritis.

2.2.5 Anti-Infectives

The US$42B global anti-infectives market (excluding vaccines) consists of three different segments: antibacterials (2004 revenues of approximately US$27B), antivirals (about US$10B) and antifungals (US$5B). The antibacterials market consists of the US$9B drug-resistant hospital infection market and the US$18B community-acquired infection market. The best growth opportunities are in the hospital market, where the problem of drug-resistant pathogens such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant *enterococci* is particularly acute. There is a pressing need for antibiotics with novel mechanisms of action and for rapid pathogen diagnostic tests, which would simplify the development process and lead to pathogen-specific or narrower-specific antibiotics. The antiviral market is expected to double by 2010, dominated by therapies for HIV and hepatitis B and C as these are the most commercially important viral infections with potential for long treatment duration. Antiviral drugs against respiratory infections such as SARS also offer potential, but such illnesses have proved challenging because of their narrow treatment windows and often indistinguishable symptoms. The influenza segment of the market may decline if there is increased focus on vaccines. For antifungals, the greatest opportunity is for drugs that can overcome limitations of narrow spectrum of activity, of formulation (e.g., some can be administered only by IV), and of toxicity (e.g., drug interaction issues with immuno-compromised patients). Novel antifungal drugs with new mechanisms of action are needed, due to the increasing number of immuno-compromised patients (cancer, HIV, solid organ transplants) and diabetics at risk of developing severe fungal infections, and the development of fungi strains that are resistant to existing drugs.

2.2.6 Tissue Engineering

Tissue engineering has potential applications in a number of areas: skin substitutes, orthopaedic cartilage and bone replacement, cardiovascular disease, neurological disorders, organ replacement/regeneration, muscle repair, and soft tissue replacement. However, only tissue-engineered skin and cartilage products have been commercialized to date. It will be at least 10 to 15 years before the technology is sufficiently advanced to make a major impact in the other categories. Further, market growth will depend on the development of new regulations for these products, which overlap between biologics and devices. Tissue-engineered products are also likely to be very expensive, so commercial success will hinge on the particular niche application. Strong economic evidence will have to be supplied supporting the products' benefits.

The first tissue-engineered products on the US market were skin substitutes for the treatment of burns and hard-to-heal chronic wounds such as pressure ulcers, diabetic ulcers and venous ulcers. This segment of the active wound management market (total global sales of some US$400M) also includes antimicrobials, growth factors and enzymes — products aimed at stimulating the biological processes of wound healing. Approximately 80% of chronic wounds can be treated with traditional or advanced dressings and ointments; in principle, therapy-resistant wounds can be treated with skin transplants or tissue engineering. The $US40M sales of the first products fell far short of their $300M forecast, resulting in the bankruptcy of the two leading players. Regulatory issues delayed the products' launch and they were very expensive, severely restricting reimbursement and market demand. Their technical limitations (short shelf life, time-consuming methods) discouraged physicians from using them. Much work is required to bring costs down, to make them more user-friendly, and to define the optimal regimen of therapy, i.e., the number of applications, at what intervals, at what time. Methods that can identify which patients require such intervention would also help expand the market.

The cartilage market is presently dominated by autologous chondrocyte implantation (ACT), originally developed in 1994, targeting defects in the knee joint due to traumatic injury. Excluding surgery and hospitalization, worldwide sales are of the order of US$20 – $40M. The surgical technique employed in classical ACT can only treat traumatic injuries of the knee, not hips or shoulders, but the majority of joint defects, particularly in the elderly, are due to osteoarthritis or rheumatoid arthritis. Matrix-induced ACT, which has recently become clinically available, could expand the market by being able to treat osteoarthritis defects in the knee and possibly cartilage defects in other joints. In addition, new products in preclinical development combine cartilage and bone, opening the market where both treatments are required. The size of these additional opportunity areas is estimated to be between US$300M and $1B, depending on the source.

Potential bone applications include jaw bone surgery, periodontal surgery, treatment of defects from osteoporosis and bone tumours, and the 10% of bone fractures that cannot be treated with standard therapies such as screws or plates because the damaged sites are too large, resulting in the need for bone grafts or synthetic bone fillers. Annually, more than 800,000 autologous bone grafts are performed worldwide. The global market for bone and synthetic materials is around US$300M, but it is unlikely that tissue engineering can capture a significant portion of this market. The technology is not far enough advanced to provide large bones with the required biomechanical properties, and in most cases existing treatments fulfill clinical needs satisfactorily. The most likely applications in the medium term will be niche areas such as dental and maxillofacial surgery, areas in which the Japanese are making significant investments.

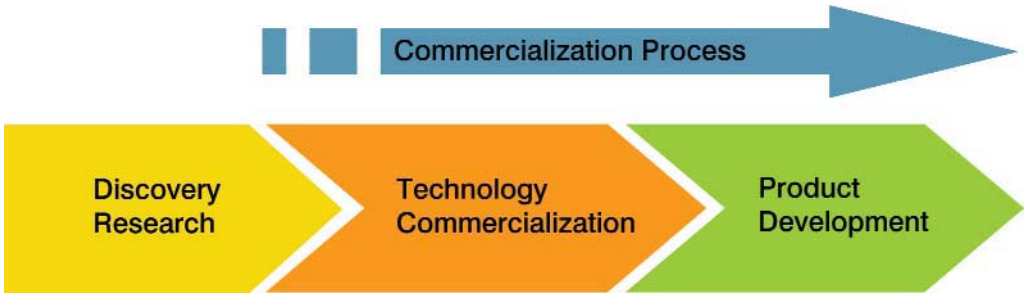
Potential applications for cardiovascular tissue focus on research in three main areas: heart valves, grafts on narrowed blood vessels, and cell grafting into the heart muscle after myocardial infarction. No tissue-engineered cardiovascular products are on the market and none is expected this decade. More than 175,000 valve replacements are performed each year, resulting in a global market valued at US$900M. Existing mechanical or biological tissue valves have problems such as durability, thrombogenicity, or shortage of supply, all of which tissue-engineered valves could address. Approximately 800,000 bypass grafts are performed annually in the US and the EU. While autologous or synthetic grafts work well when the graft's diameter is larger than 6mm, smaller diameter vessels are more difficult to create and lack the elastin structure of a native vessel, so that they become occluded by thrombosis very quickly. Initial studies with injected skeletal muscle cells for the regeneration of injured myocardium tissues show promise but will have to overcome several hurdles before cell transplantation will be suitable for long-term therapy. Such hurdles include the intrinsic differences in contractile properties between the cardiac and injected cells and the requirement that the cells be electrically coupled to the rest of the heart.

Approximately 42,000 organs were transplanted globally in 2001; half were kidneys, followed by liver (11,000), heart (4,600), lung (2,000) and pancreas (1,500). The longest waiting times are for kidney and heart-lung transplants. Despite high medical needs, the engineering of complete organs is a long way from market reality. More likely to be developed first are organs whose function can be replaced by cell therapies (e.g., encapsulated islet cells in the pancreas for diabetics) and bioartificial liver-assist devices that may provide an opportunity for the liver to regenerate itself, depending on the severity of the disease.

2.3 Stages of Drug Development

The first step of this process is the commercialization of the technology: opportunities for commercial innovation are evaluated, nurtured through a series of steps to bring the ideas to a point where new start-up companies are established and capitalized or the invention is licensed out or sold. Next comes product development, which encompasses all aspects of product and manufacturing development, culminating in market sales (Figure 3).

Figure 3: Stages of Drug Development



Source: TRM Steering Committee.

2.3.1 The Drug Discovery Process Today

Access to new technology and the investment required to produce new discoveries is one of the key drivers of this industry. The primary purpose of the discovery process is to identify and select novel drug candidates that can enter product development. In other words, the technologies are used to answer the fundamental question of whether a drug candidate is worth developing. In the traditional drug discovery process, in which the chemists synthesize new structures and subsequently test them in biological systems, the rate-limiting step was the identification of targets. Today, the situation is reversed: an increasing number of identified drug targets in search of compounds that offer therapeutic benefits. *The bottleneck in drug discovery is now selection of the right target for drug development. The need to produce fully validated targets is critical for two reasons: firstly, to select from increased number of targets; secondly, because only a limited number of candidates can be developed in the more expensive development phase.*

2.3.2 Product Development

Because of the large number of potential products and the government-regulated requirements for systematic and high quality research, developing new biopharmaceuticals has become a risky, time consuming and expensive undertaking. The process must follow a staged, systematic approach including research (basic and applied discovery), pre-clinical, clinical (Phases I, II and III), manufacturing and post-marketing (Phase IV). The process can take eight to 15 years (Figure 4) and cost approximately US$800M.

Figure 4: Stages of Drug Product Development

Source: TRM Steering Committee.

The first regulatory filing for a potential new drug candidate is the investigational new drug (IND) status. Obtaining IND status means that the company has provided enough data on animal pharmacology, toxicology, the manufacturing process, pharmacokinetics and the proposed clinical trial design (Table 14) to demonstrate that it is safe to begin human clinical studies. The primary objective in clinical research is to demonstrate that the drug is safe and efficacious. Phase I studies are used to assess safety, collect human pharmacokinetic data and fine-tune the dosing regimen. Phase II studies expand on Phase I and test for any safety concerns and efficacy of different dosages in patients with the disease. Phase III studies are the largest and have the most scientifically rigorous study design. Large numbers of patients with disease are tested to statistically demonstrate the benefit/risk profile on a drug intended for wide public use.

Once a company has assembled sufficient non-clinical and clinical information, it files a new drug application (NDA) (in the US) or a new drug submission (NDS) (in Canada) with regulators. If the data concerning drug safety and efficacy and manufacturing safety and process are adequate, an approval to market is allowed. In certain cases post-marketing studies are required for marketing approval; the manufacturer must continue to test for any safety or efficacy concerns and to monitor adverse drug reactions in a large population base. The table below illustrates the stages of the drug development process and the challenges to be met at each stage.

Table 15: Product Development for Biopharmaceuticals

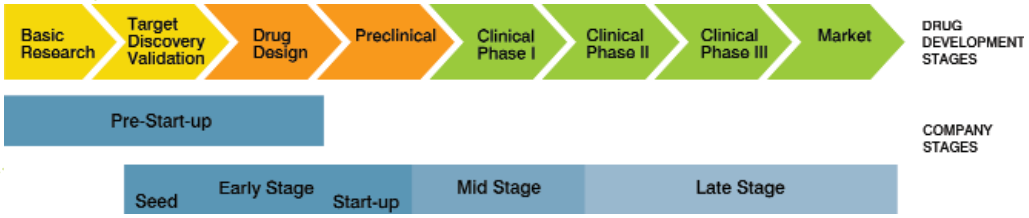
	Research	Pre-Clinical Studies	IND	Clinical Studies			
				Phase I	Phase II	Phase III	
Objectives	Discover, screen and select product candidates for product development	Safety and efficacy to permit extending testing in humans	Approval to start human clinical testing	Safety and efficacy in humans	Safety and efficacy	Efficacy and safety	Approval to market
Data	Molecule identification, Target validation, Screening, Drug design	Toxicity, Pharmacology, PK in animals, Initiate manufacturing process, plans for clinical studies	IND	Pharma-cology, PK, Dosing in humans	Similar to Phase I, Short term toxicity, with dosing varia-tions to test efficacy	More detailed efficacy and safety data with larger numbers of patients with disease to statistically show overall benefit and risk profile	NDA NDS
Study Design	Laboratory/ animal	Animal and laboratory studies		20-80 health volunteers or patients Open label study	50-200 patients with disease Open label controlled	100s to 1000s of patients with disease; randomized, controlled, double blind, multi-centre.	
Duration	2-10 years	4-6 years	30 days	1-2 years	2-2.5 years	2-4 years	1-2 years
Manufacturing	Development of manufacturing specifications and processes continues throughout development						

IND = investigational new drug; NDA = new drug application;
NDS= new drug submission; PK = pharmacokinetics.
Source: TRM Steering Committee.

2.3.3 Linking Drug Development and Commercialization

Companies in the process of commercializing technology are typically referred to as pre-startup, early, mid and late stage, depending on their level of progress in the commercialization continuum (Figure 5; Table 16).

Figure 5: Correlation of Drug Development and Company Growth Stages



Source: TRM Steering Committee.

The *pre-start-up research stage* is the period of basic scientific discovery, which is the foundation for innovation. It represents the discovery of new knowledge and opportunities that can be exploited. Commercialization begins in the pre-seed research phase with ideas for potential commercial use of the technology, possible product ideas and invention disclosures. This usually occurs in universities, institutes, incubation centers and in companies doing discovery research.

Early-stage companies are established to commercialize research discoveries. This transfer of technology from the original researchers in universities usually occurs through the university innovation liaison offices (UILOs). Successful ideas reach the Seed Stage where they receive capital to pursue the product ideas further. The key focus at this stage is to protect IP, identify product candidates, show proof-of-principle and initiate market assessment. Finally, the Start-Up Stage is reached and the new company is provided with capital to begin recruiting key staff, identify more product candidates and undertake development. This research is sometimes performed at universities, but is mostly done at the start-up companies. Early-stage start-up companies generally have few employees and were founded by the original researchers. It is generally recognized that the structure for applied research has to be distinguished and separated from the universities' discovery research labs. This will maintain the culture needed for commercialization, which requires that applied research be product development-based and on a rapid timetable of completion to ensure competitiveness. This principle also applies to efforts to capitalize on IP.

Mid-stage companies in the process of scaling up product development represent the longest, most costly and complex stage during which the greatest increase in value will occur. The process can take from five to 12 years. These companies are establishing the preliminary commercialization conditions for IP protection, and proof-of-principle research to justify further development.

Late-stage companies are generally involved in more expensive Phase II and III clinical testing in humans and the complexity of regulatory and manufacturing issues. These companies require considerably more capital and skilled personnel in the management, clinical research and regulatory fields.

Table 16: Stages of Company Development and Drug Development

Stage	Description	Drug Development Stage
Research Stage	*Basic Research Stage*. This constitutes the period of basic research in new technologies and ideas. It is usually conducted in universities or sites of excellence.	Discovery Research -New technology -Target identification
	Pre-seed or Commercial Idea Stage. The identification of the potential commercial use of research and the preparation of additional applied research to firm up the potential. Period of invention disclosures.	Technology Commercialization -IP protection -Technology transfer -Target validation -Preclinical studies
Early Stage	*Seed Stage*. Researchers of companies receive initial capital to support the development of ideas in a project and undertake proof-of-principle studies, IP review and strengthening, preliminary market assessment or development of initial product. Assists in moving a project from an academic level to a greater corporate structure. In Canada, this activity is often postponed to the start-up stage.	
	Start-Up Stage. Companies in late discovery to preclinical testing level.	
Mid Stage	*Scale-up*. Companies with a defined product and use in late preclinical or entering Phase I to early Phase II clinical trials.	Product Development -IND -Clinical trials -Manufacturing process -NDA
Late Stage	*Scale-up to manufacturing and marketing*. Companies in late Phase I to Phase III clinical trials, or building manufacturing or infrastructure for commercialization.	Development complete

Source: TRM Steering Committee.

To achieve the return on investment needed, access to global markets should occur quickly. This requires knowledge of regulatory approval processes in key countries, as well as market knowledge and access. Because of the high barrier to entry for these processes, biotech companies will enter strategic alliances for this access, usually with large pharmaceutical companies. Such alliances are also used to fund the costly Phase III clinical testing. Depending on the nature of the alliance the value-added benefit of manufacturing could be lost to foreign companies or countries. Increasingly, Canadian products are not manufactured in Canada.

The key to growing the Canadian biopharmaceutical industry is one of attracting investment.

2.4 Issues around Investment Attractiveness

Investment attractiveness factors also affect the success of commercial development. These generally include items affected by government policy, such as tax incentives, tax rates, business costs, regulatory requirements, government priorities and social attitudes.

2.4.1 Business and Tax Environment

A recent Ontario Biocouncil Report found that different factors are valued depending on the stage of company development of the company.[79]

- Young biotechnology firms valued commercialization factors such as access to venture capital (VC), proximity to world-class research institutions, incubators and local highly-skilled labour pools, infrastructure and government support.
- Mature biotechnology firms valued investment attraction factors such as inexpensive land, the ease of acquisition of building and operational permits, low business costs, tax incentives, clinical trials infrastructure and favourable regulatory environments.

The Scientific Research and Experimental Development Tax Credit

One of Canada's biggest levers in this area is the SR&ED Program, a tax incentive of the federal and provincial governments designed to support and foster science and technology, particularly R&D conducted by companies in Canada. Compared with other countries, Canada has one of the most generous systems of R&D tax incentives and income tax treatment in the world. The table below sets out the main features of the program.

Company	Tax Credit
Canadian-controlled private corporations with taxable income of $200,000 or less	-35% investment tax credit on first $2,000,000 of SR&ED expenditures (20% on amounts above $2,000,000). -Can deduct 100% of current and capital expenditures incurred or SR&ED in Canada.
Large corporations	SR&ED expenditures generally qualify for 20% tax credit.

Recently, there have been recommendations for improved government support, such as refundable SR&ED tax credits for public companies or the use of flow-through shares. The latter tax incentive is available to mining and petroleum companies to help unprofitable firms raise capital by transferring their unused deductions for exploration to individual shareholders. BioQuebec has suggested a tax credit program on IP cost. Many stakeholders continue to call for more incentives to increase the supply of risk capital.

Low Input Costs

KPMG annually assesses the cost of doing business around the world. In five consecutive reports, Canada ranks as the lowest-cost G-7 country in which to conduct business. According to the 2004

[79] Report of the (Ontario) BioCouncil (March 2002), especially Chapter Two.

and 2006 KPMG Competitive Alternatives International Business Cost studies.[80]

- Canada holds a significant cost advantage relative to the US.
- Canada is the most cost-competitive G-7 country in seven of the 11 industry sectors, including electronics, pharmaceuticals and specialty chemicals, as well as biotechnology R&D, clinical trials, software development and corporate services.
- The analysis takes into account labour, transportation, energy, facility costs, and income and non-income taxes.

- Canada has increased its cost advantage over the UK and other European countries since 2002.
- Compared with the US, Canadian costs are significantly lower for technical/professional labour and senior management.
- Montreal is the international cost leader in 15 of 17 industry sectors.
- Canada has the best G-7 corporate tax rate for R&D operations.
- Canada offers the lowest costs in the G-7 for industrial land and construction, as well as for telecommunications.

Regulation

Government is also responsible for establishing the regulatory requirements that biopharmaceutical testing and manufacture must meet to demonstrate effectiveness and safety. Every advanced country has a similar regulatory regime. These are onerous requirements: they impose heavy costs on development for the conduct of clinical trials and for manufacturing specifications that meet the demands of numerous key markets internationally. Failure to do so costs time and money. The design of regulatory rules and lack of support for regulatory authorities can also delay the speed of development, imposing additional costs. For biopharmaceuticals, speed of development to minimize time to market is an important criterion for competitiveness. Industry participants have repeatedly maintained that Canada should improve its speed of regulatory approval. This should include both improved drug approval times and faster approval to conduct Phase I–III clinical trials.

Canada has one of the longest average drug approval times, upwards of 600 days as compared with the EU's 200-300 days and 400 days in the US.[81] With an increasing number of new products coming to the market, these times may lengthen unless attention is given to improvement. Approval delays create an unfavourable business climate for commercialization. Although product approval times are very important to branch plant companies with drug manufacturing and marketing organizations, they are not as critical for developing companies. The latter need rapid approval of clinical trials and manufacturing facilities, since they affect speed and cost of development.

[80] KPMG (2006), Competitive Alternatives: KPMG's Guide to International Business Costs, Executive Summary and Vol. 1, tables.

[81] Canadian approval times appear in Health Canada (2004) Regulatory Review of Pharmaceuticals, Biologics and Medical Devices, Annual Summary of Performance, pp. 24–25. US approval times are given in US Health and Human Services, Food and Drug Administration (2004) Report to the Nation, Improving Public Health Through Human Drugs, Chapter 1, Drug Review, pp. 14-16; EU times are in the European Medicine Agency (2004) Tenth Annual Report of the European Medicine Area 2004, EMEA/61492/2005/EN/FINAL, pp. 31-32. Note that the UK scientific review of new active substances is now 40 days; see Medicines and Health Care Regulatory Agency Annual Report and Accounts 2004/05, p. 30. Comparisons are difficult because rates depend on application rates and types of application. Biologics generally require longer approval times.

Slower approval times can greatly delay a company's ability to show value in its technology, enough to induce a Canadian company to conduct clinical trials elsewhere. Choosing to conduct studies in other countries deprives Canadian clinicians of early access to Canadian developments, as well as to the income for conducting the trials. The delay in approval times also leaves an impression that Canada is less friendly to innovation. The government appears intent on addressing this issue, since it has announced repeatedly it is improving timeliness of regulatory process for human drugs and for biotechnology regulation.

Canadian pharmaceutical companies must develop drugs for global markets and meet global standards. Most biopharmaceutical companies will seek their first marketing approval for a new drug in the US and EU because of access to the world's largest markets. This is necessary to generate revenues and justify the high cost of development. *It may be time for Canada to consider an integrated approval process with the US, given that biopharmaceutical development is designed to be competitive globally and to meet global standards for safety and efficacy.*

As part of its improvement of regulatory processes, the government must examine the issue of international harmonization, so that Canada can maintain its level of exports and support Canadian companies who undertake clinical studies in other countries. Currently, Canada is involved in a number of international initiatives aimed at examining the harmonization of regulations. One such initiative is the "International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use", on which Canada has observer status. Harmonization requires that the country of origin inspect and provide a manufacturing certificate of compliance to a foreign for any Canadian company that wants to pursue clinical trials in the foreign country. It is important that Canada meet this requirement in a timely manner in support of Canadian based companies to allow them to move development forward rapidly.

Clinical Research Infrastructure

The conduct of clinical trials is one of the most expensive costs of development. Consequently, speed of clinical trial development, availability of patients and the support organizations to conduct clinical trials greatly affects the success of development. This has now become an area of global competition. More countries are entering this area of drug development, their competition eroding Canada's advantages in this area.

2.4.2 Political Attitudes

The government of Canada is clearly supportive and focused on improving Canada's performance in the high knowledge industries of the future. In February 2002, the government released its Innovation Strategy in two papers. Both examined what Canada must do to ensure equality of opportunity and economic innovation in the knowledge society. Former Prime Minister Paul Martin identified "Building a 21st Century Economy" as a top priority of his government. More recently, the Minister of Industry, Maxime Bernier, indicated that "boosting Canada's competitiveness and prosperity is a top priority for this government".

2.4.3 Social Attitudes

There is considerable public concern about biotechnology and biopharmaceuticals, which can threaten some developments. A large portion of this is due to concern over genetically modified foods as opposed to biopharmaceuticals. The demand for regulation and caution is growing. For instance, 37% disagree with the proposition that "government should encourage biotech although there may be unknown risks". Other results in this area include:

- 4% more agree with the idea of "government regulating biotech more than other sectors" (73% now agree);
- 4% more agree with the idea of "conducting further research into long-term health and environmental impacts before allowing any further use of biotech" (87% now agree);
- 5% more agree with the idea of "slowing use of biotechnology until more is known" (72% now agree); and
- about 10% more disagree with the idea that "enough is known about safety of products made through biotechnology to allow them to be used" (54% now disagree).[82]

2.5 Industry Structure and Capitalization

The Canadian biotechnology industry is well positioned to help Canada succeed and lead in the increasingly competitive global environment, provided it addresses some key weaknesses. These are first, to improve the technology transfer process so as to insure that IP is strongly protected; second, to reinforce efforts to obtain experienced managers; third, to focus capital at the stages where these weaknesses exist. The following offers a snapshot of the industry:

- Canada has generated more than twice as many biotechnology companies proportionately to the US. This is positive in the sense that innovators are oriented to commercializing new discoveries. It generates weaknesses, however, in that small companies must share available financial resources. Evidence is presented later that Canadian companies may have been started prematurely, weakening their competitive position.
- Most companies are small, with 352 or 72% having less than 50 employees; of these, 243 have less than 10 and 153 less than five employees. Many of the small firms receive only seed or angel capital, and operate within government or educational institutions. Their ability to grow is limited and the turnover rate is high. Medium-size companies (50-149 employees) and large (>150 employees) account for 15% and 13% of the number of companies (Table 17 below).
- Large companies, representing only 13% of the firms in 2003, account for 64% of biotechnology revenues, but only 20% of R&D expenses. Medium-sized firms accounted for 24% of revenues and 47% of spending on R&D. Small firms accounted for 12% of revenues and 33% of R&D expenses.
- The biotechnology segment has been growing consistently for several years. In 2003, there were 490 innovative biotechnology firms in Canada, a 31% increase from 375 in 2001 and a 74% increase from 282 in 1997. Combined, these 490 companies generated revenues of $3.8B in 2003. Their spending on R&D also increased to $1.5B. Despite an increase in the number of firms, the number of employees working in biotechnology activities remained stable at about 12,000.

[82] Canadian Biotechnology Strategy: Public Opinion Research into Biotechnology Issues—Fifth Wave, (December 2001).

- A majority of Canadian biotechnology firms (53%) focus on human health.
- In 2003 more than 74% of the innovative biotechnology firms were concentrated in the three most populous provinces: Quebec (30%), Ontario (26%) and British Columbia (19%). On a per-capita basis, Quebec, BC and the Prairies have about twice the number of companies as Ontario, Alberta and the Atlantic provinces. More than 85% of 2003 revenues were earned in the provinces with the most companies. Ontario dominates with the highest revenues (53%), followed by BC (20%) and Quebec (13%).
- Ontario firms led the way in biotechnology revenues. Quebec accounted for the largest share of biotechnology firms, employees and R&D spending.
- 85 of the firms (17%) are publicly traded and have a market capitalization in 2003 of about $18B. The 10 leading companies represent about 70% of the total market capitalization.
- From 1997 to 2003, biotechnology exports nearly tripled from $311M to $992M.

Table 17: Distribution of Canadian Biotechnology Companies by Region, Size, Employees and Revenues, 2003

	Innovative Biotechnology Companies	Employees with Biotechnology-related Activities	Biotechnology Revenues (C$M)	Biotechnology R&D Expenditures (C$M)
Region				
Canada	490	11,863	3,842	1,487
Quebec	146	3,700	480	490
Ontario	129	3,508	2,026	453
Manitoba	21	1,213	145	56
Saskatchewan	34	337	94	23
Alberta	44	727	298	88
British Columbia	91	2,173	779	370
Atlantic	25	206	21	7
Size				
Small (0–49 employees)	352	3,619	468	495
Medium (50–149 employees)	77	3,746	909	699
Large (150+ employees)	61	4,498	2,466	293

Source: Statistics Canada, Biotechnology Use and Development Survey, 2003.

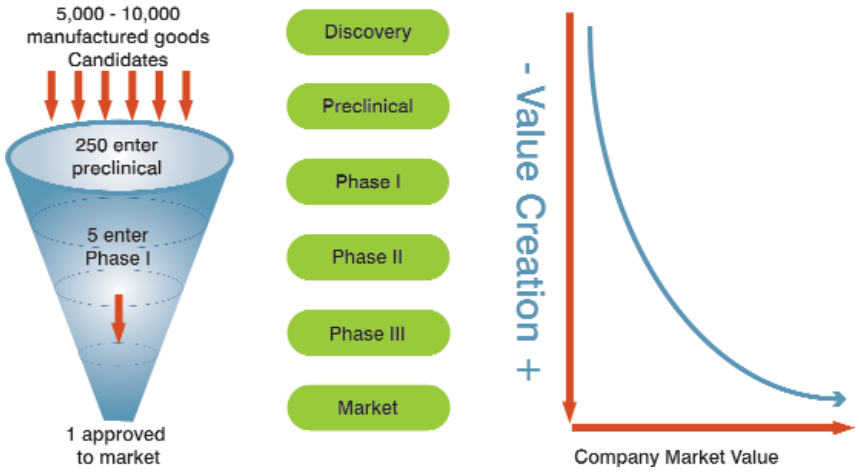
2.6 Understanding Company Valuation: The Biopharmaceutical Value Chain

An important concept in understanding the development and valuation of biopharmaceutical companies is the value chain (Figure 6). The majority of development companies are net users of capital until they develop products or services. As potential products successfully move from the research stage to a marketable product or service, the value of the company is increased and the risk of development is reduced. This value is represented in the capitalization of the company. The value represents the expectations of future commercial value and the probability of success. Consequently, as products move up the development path, the number of candidates in development is reduced to a

selection of the best, and the probability of marketing a product increases. This increase in value justifies the large increases in capital provided to companies as they grow.

One problem in commercialization is that Canadian biotech firms are undercapitalized. As the table below shows, the whole industry had 2003 revenues of about $3.8B, about enough resources for it to commercialize two or three drugs to success at a global level.[83]

Figure 6: Value Chain — Risk, Valuation and Product Success of Development



Source: TRM Steering Committee.

Yet as noted earlier (Canadian Product Pipeline by Phase, Table 3) the Canadian pharmaceutical industry has in fact 14 drugs on the market, 16 additional drugs submitted for regulatory approval and another 42 at Phase III clinical trials.

Table 18: Biotechnology Sector Statistics

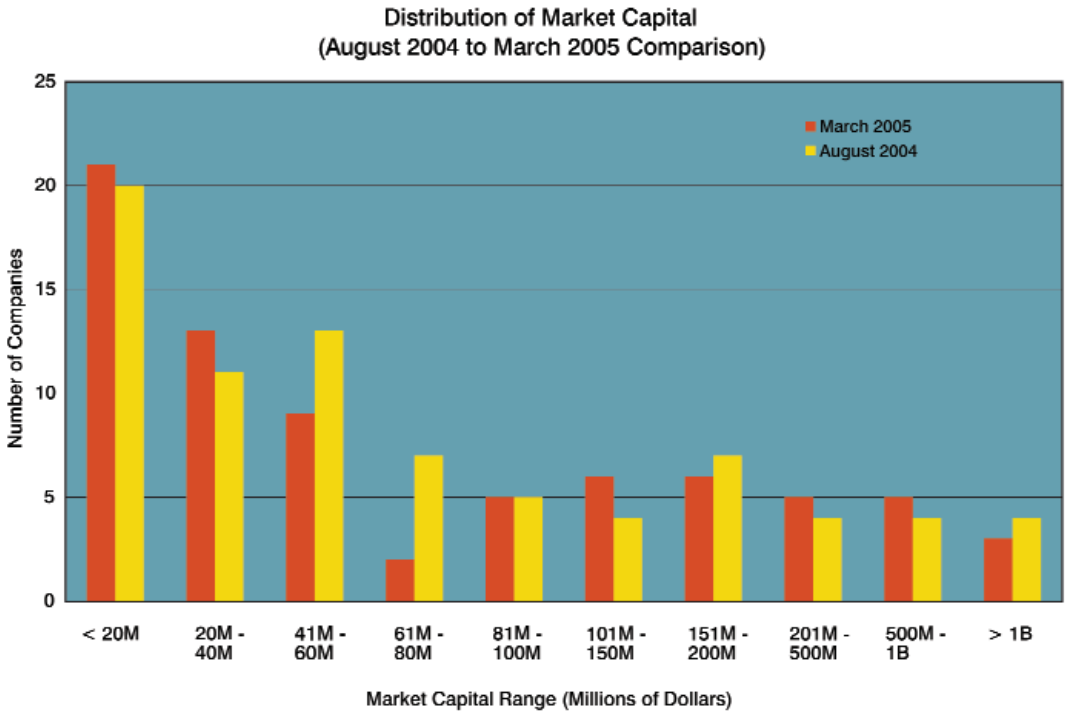
Year	Number of Firms	Total Revenues (C$M)	Total R&D Expenses (C$M)	Total Employees
1997	282	813	494	9,019
1999	358	1,948	827	7,748
2001	375	3,569	1,337	11,897
2003	490	3,821	1,487	11,931

Source: Statistics Canada Biotechnology Use and Development Survey, 1997, 1999, 2001, 2003.

[83] The Research-Based Pharmaceutical Manufacturers Association of Canada (R&D) estimates it costs $1.3B to bring a new drug to market. "Facts you should know", R&D, website at www.canadapharma.org/home_e.htm

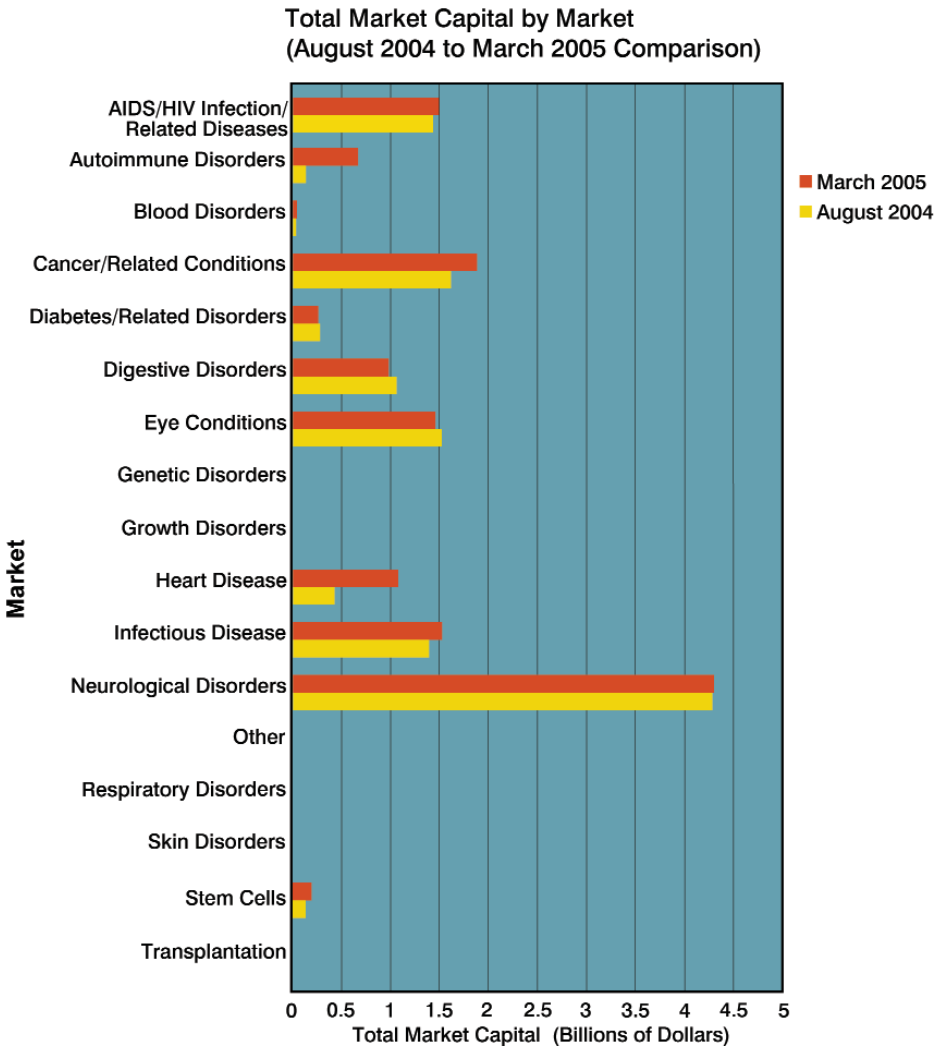
Other studies, looking at publicly traded companies, show the profile of industry capitalization, with most firms (about 50) capitalized at $100M or less and only three at $1B or more. The amounts shown in Figures 7 and 8 below sum to about $750M, the total for amounts actually spent at each stage of drug development. But the total cost must take into account the amounts spent on drugs that fail at some stage of product development. The winners have to pay for the losers. Hence the difference. This suggests that of the 490 or so biotechnology firms in Canada, only three have the scale to grow into a multinational company. Figure 8 indicates the amount of capitalization by therapy. As is evident, some of the most promising areas of research have not exactly captured the imagination of investors and become springboards for great enterprises capable of commercializing those discoveries at world levels.

Figure 7: Distribution of Market Capital



Source: Industry Canada, Peter Winter, ed., Biopharmaceutical Pipeline in Canada, March 2005, No. 2.

Figure 8: Total Capitalization by Therapy



Source: ibid.

To be sure, capitalization is only one measure of company capacity as a drug development platform. Yet it is interesting to compare the structure of the Canadian industry with that of the US, if only because Canadian firms are, like US firms, primarily developing drugs for the North American market, and in theory at least, can draw their capital from the same capital pools in an increasingly integrated continental market. Canadian sales revenue is roughly 11% of US sector sales, and R&D spending is around 9% of US levels — suggesting that Canadian companies are operating within Canada at about the same level as US companies, which operate in a home economy 10 times greater than Canada's. Examining the capitalization ratios reveals a striking difference, however: US biotechnology firms are capitalized at a level 38 times greater than those in Canada. Moreover, the ratio of the number of Canadian companies to the number of US companies is about 25%, suggesting that Canada has about twice the total number of biotechnology companies in proportion to the size of its economy as the US.

The table below compares Canada to the US and Europe. Compared to Europe, too, Canadian companies are less robust platforms for commercialization of their discoveries.

Table 19: Comparison of US, European, Canadian Biotech Stats (YE 2004) ($US)

	Ratio USA:Canada	USA	Europe	Canada
Sales Revenue[1]	12	$42.7B	$7.3B	$2.1B
Annual R&D[1]	20	$15.7B	$4.2B	$0.8B
Number Companies[1]	3	1,444	1,815	472
Number Employees[1]	19	137,400	25,640	7,370
Number of Public Cos.[1]	4	330	98	82
Market Capitalization[2]	34	$466B	$26B	$14B

Sources:
1. *Beyond Borders, The Global Biotechnology Report, Ernst & Young, June 2005. www.ey.com/global/content.nsf/International/Biotechnology_Report_2005_Beyond_Borders*
2. *Biotech 2005, Industry Review and Outlook, Burrill & Company, October 2005. www.burrillandco.com/pdfs/gsb_laguna_2005.pdf*

Understanding why the structure of Canada's biotechnology industry poses such a development problem requires a grasp of how the industry creates value and the special conditions under which it operates.

2.6.1 Geographic Concentration (Clusters)

Concentration of high technology companies with supporting services in geographic locations or clusters is highly correlated with industry competitiveness. Clusters increase the productivity of companies, drive the pace of innovation and encourage the formation of new businesses. These clusters provide conditions for:

- a strong academic base with high-quality, world-class research;
- the environment for translation of research output to commercialization;
- an adequate labour and knowledge pool in scientific and business development;
- an appropriate industry infrastructure;
- opportunities for collaboration and alliances;
- protection of IP;
- availability of equity and finance; and
- a positive government policy towards the industry.

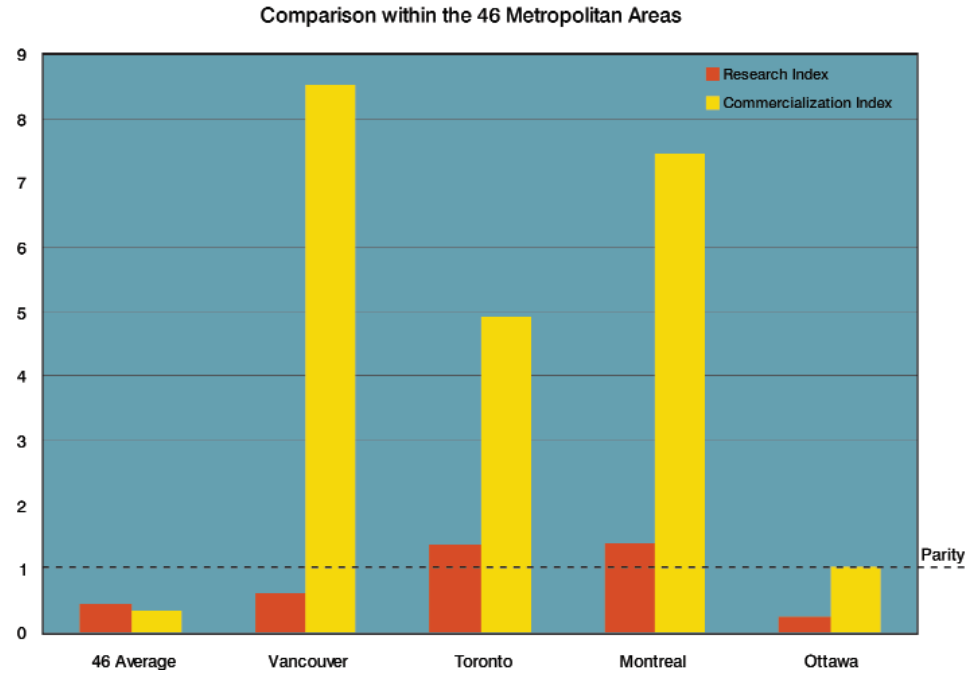
The federal government has recognized the importance of clusters for commercialization, by including in the government approach to innovation, the goal of working with local communities to stimulate the creation of more clusters.

In the US, nine major leading biotechnology clusters (of the 51 metropolitan areas) are leaders because they have sufficient concentration of innovative companies around strong research capacity in universities or government labs, have access to continuing private sector investment in product development, and have consistently demonstrated the ability to convert research into successful new biotech businesses. Five of the top nine clusters — the leaders (Boston and San Francisco) and three other areas in which biotechnology is growing rapidly (San Diego, Seattle and Raleigh-Durham) — account for the bulk of the growth in new firms. Together they account for 75% of venture funds, 74% of value of research contracts and 56% of new biotechnology businesses. Thus far, none of the other

42 largest areas in the US has developed a significant concentration of biotechnology activity.[84]

Cluster growth could help address the weaknesses identified here for Canadian biotechnology companies, since clusters afford firms the requisite concentration of people with commercialization skills, capital and IP expertise. Moreover, they allow for two-way communication between academics and business. Clusters are present in all provinces and all major cities in Canada. However, four provinces at present have the largest concentration of companies in the biopharmaceutical sector, which compares favourably in terms of number of companies with the major biotechnology states in the US.[85]

Figure 9: Comparison of Canadian Clusters with the 46 US Clusters



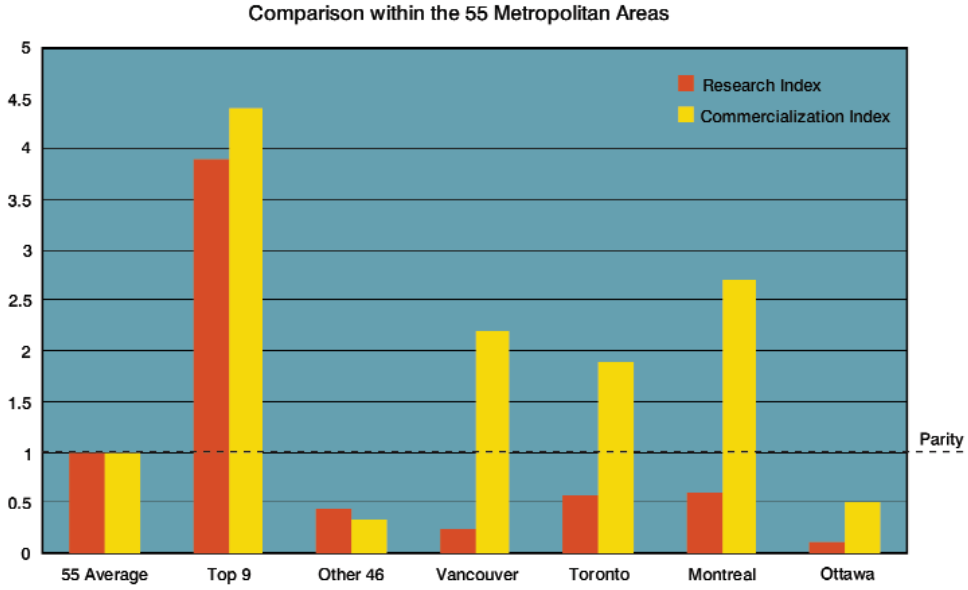
Source: ICT/Life Sciences Converging Technologies Cluster Study: A Comparative Study of the Information and Communications, Life Sciences, and Converging Next Generation Technology Clusters in Vancouver, Toronto, Montreal and Ottawa, (January 2005).

It is beyond the scope of this report to undertake a complete review of all clusters in Canada and their potential. However, a recent study compared four Canadian clusters (Montreal, Ottawa, Toronto, and Vancouver) with those in the US. The comparison was based on a set of research criteria (amount of research funding, number of patents) and a set of commercialization criteria (venture capital, value of research alliances, new firms and firms >100 employees). The four Canadian clusters do well against the average of the 46 smaller clusters on both research and commercialization indices.

[84] Joseph Cortwright and Heike Mayer, Signs of Life: The Growth of Biotechnology Centres in the US, The Brookings Institution Center on Urban and Metropolitan Policy (2002), p. 5, Executive Summary.
[85] Ernst & Young, Beyond Borders (2005), Top Biotechnology Centres.

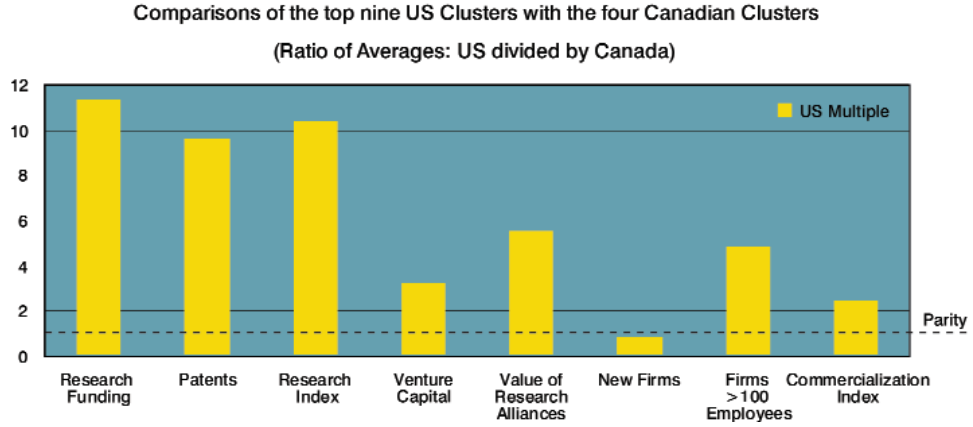
However, if the nine key US clusters are included in the average, these nine key clusters do much better than the Canadian clusters (Figure 10). Three of the Canadian clusters are competitive on commercialization indices, but not on the research indices.

Figure 10: Comparison of Canadian Clusters with All 55 US Clusters



Source: ibid.

Figure 11: Comparison of Canadian Clusters with the Nine Key US Clusters



Source: ibid.

If Canada is compared with the key US clusters, the US Research Index is 10.3 times higher and the Commercialization Index is 2.4 times higher than the Canadian clusters (Figure 11).

Thus the nine key clusters would be the main competitors, since they outperform the Canadian clusters, moreover, the US clusters are more mature. The Province of Ontario, for instance, only recently announced its Biotechnology Cluster Innovation Program and established its commercialization centre MaRS. Canada still has some distance to travel before its clusters match the performance of the leading US biotechnology centres.

The Toronto and Montreal clusters have the potential to match the key US clusters because they have the research capabilities, diversity and staying power, while nurturing emerging clusters over the longer term. Toronto, for example, has the largest faculty of medicine in North America and the output of peer-reviewed publications from this area, as listed in MEDLINE, is greater than any other medical centre in the world. The Hospital for Sick Children also has Canada's largest computing facility dedicated to biological research.

2.7 Key Drivers of the Biopharmaceutical Industry

Knowledge-based industries, like biopharmaceuticals, have distinguishing characteristics compared to traditional industries that are important for their success. They are:

- technology and science driven;
- provide high rates of growth;
- yield high rates of return on equity;
- maintain a global orientation;
- require human skills in technology and business development;
- need longer term, patient risk capital to complete development, since debt capital is inappropriate; and
- require the participation and collaboration of the primary stakeholder segments, including the R&D experts in universities and government labs, industry members, the government and investment communities.

The major drivers for successful biopharmaceutical innovation have been identified in several studies. They include:

- global market demand;
- access to technology;
- access to risk capital;
- human scientific and business skills;
- effective technology transfer;
- clusters and incubators to nurture development;
- investment attractiveness; and
- robust IP protection.

2.7.1 Access to Technology

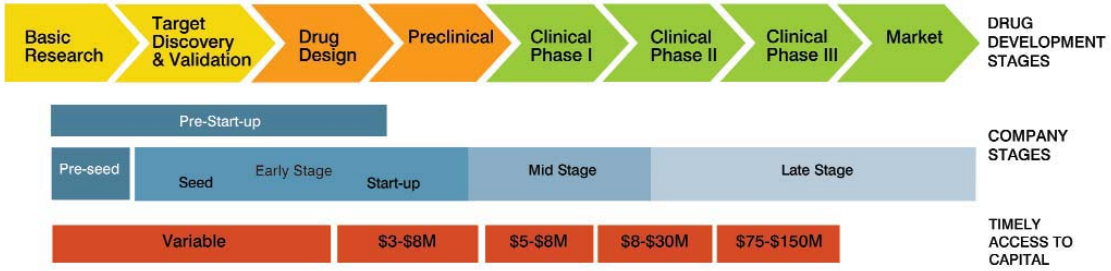
Access to new technologies and scientific advancements is the foundation for innovation opportunities. The biopharmaceutical industry relies on a large number of new discovery and enabling biotechnologies, which drive innovation and will be the source of future economic value. Most developed countries are increasing investments and developing strategies in order to capitalize on innovation.

2.7.2 Access to Capital

Drug development requires a copious flow of capital from patient investors, as it can take 8 to12 years, and millions of dollars, before a biotechnology firm can apply for regulatory approval for its first product. A typical company may require up to $2M in its first two years, rising to $5 to $10M in its second two years. Later capital requirements will depend on its therapeutic focus, number of drugs under development, and manufacturing and marketing strategies, that can amount to over $10M a year. Moreover, as development proceeds successfully, significantly larger amounts of financing are needed for later-stage clinical testing and manufacturing (Figure 12; Table 20). Due to the structure of the industry, debt financing is generally not appropriate.

The bulk of research funding comes from government and institute grants. Early- to mid-stage companies get most of their seed and start-up funds from universities, governments, angels and venture capital. Venture capital and strategic alliances provide the bulk of financing for late start-up and mid-stage companies. For a mid-stage company, the completion of Phase II clinical testing usually designates the first proof-of-principle of the value of the company's product. Late-stage companies use a mix of public equity, strategic alliances with big pharma, venture funds and some government funds. These are usually sufficient to complete development.

Figure 12: Needs by Development Stage for a Biopharmaceutical Drug



Source: TRM Steering Committee.

During the first 10 years of development, the sources of capital for biotech companies are 10% venture capital, 40% public equity and 50% big pharma.[86] However, the timing of their use of such sources is critical. In early development, venture funds are typically used to carry the company over the first critical proof-of-principle work. After this, public equity funding and strategic alliances are more common. During the early phases, low amounts of investment can create high value, so companies often employ a strategy of postponing strategic alliances and public equity until they can demonstrate value and retain a larger share of future value.

[86] Biopharmaceutical Sector Competitiveness Framework, Industry Technology Roadmap Initiative, Preliminary Work, Industry Canada (May 2000).

During the TRM Roundtable consultations with industry CEOs, the lack of risk capital for drug development was identified as a significant barrier to commercialization. To be sure, there are mechanisms to support the research phase (research grants sponsored by government) and to sustain the early development phase. However, there is a grey area of pre-seed/seed stage and of mid-stage scale-up and development for which public funds are no longer available and where private investors consider the investment too risky or too large. Those involved in commercialization do not claim that the problem of financing innovation-based new firms is a general one, but rather locate it *specifically in the transition stage after start-up*.

Table 20: Capital Needs and Source and Use of Funds by Company Stage

Stage	Research Stage		Early Stage		Mid Stage	Late Stage
	Basic	Pre-seed or Commercial Idea	Seed	Start-Up	Scale-Up	Scale-up
Investment Needed	Variable	$0.1–0.5 M	$0.5-$1.5M	$3-8M	$5-40M	$75-150M
Source of Funds	Govt and other research grants	Research grants, Individuals	Research grants, Private funds from venture capital and angels	Venture capital, University funds, grants	Venture capital, Public equity, Strategic alliances	Strategic alliances, public equity
Use of Funds	Basic & discovery research	Applied research to test commercial idea	Confirm commercializ-able proto-types and IP	Initial preclinical product testing	Scale up to meet regulatory requirements to test product effectiveness and safety. Preclinical to early Phase II stage.	Late Phase II to Phase III clinical testing; some manufacturing infrastructure

Source: TRM Steering Committee.

2.7.3 Management and Scientific Skill and Experience

A successful progression through the multiple phases of commercialization needs strong management teams with a combination of technical, financial, clinical, regulatory, business and marketing skills and experience. This includes experience in designing strategy and implementing product development plans, obtaining financing, manufacturing and marketing. *These skills are not typically available in most start-up companies, as they are initially staffed by researchers*.

Moreover, the business has to have a global orientation, since generally a company cannot justify the investment needed to develop a product solely for the Canadian market, but must gain access to the large US and EU markets. This requires knowledge and experience in international regulatory requirements, commercialization practices and foreign business operations. *The lack of experienced business managers has been identified as one of the weaknesses of Canadian biopharmaceutical companies*.

Participants at TRM Roundtables identified the largest barrier to competitiveness as the availability of experienced senior management in commercial product development and company growth. Such people guide company growth and move products through the commercialization process to the marketplace. These managers not only have to design and direct the strategic product development plan and face the technical and regulatory hurdles involved, but also have to manage manufacturing, find funding and develop alliances for commercial success.

An important point to make is that one of the most important roles of top managers is to manage the start-up company "cultural gap" as the firm transitions from research to commercialization. Most start-ups originate in the research environment of universities, where research and knowledge creation is the dominant culture. Even university industry liaison offices, which concentrate on technology transfer, are embedded in this academic mindset. Yet the success of development requires a different set of skills and experience on the commercial side — the seasoned managers mentioned above. Canada is lacking in these people because large pharmaceutical companies, where such skills are traditionally gained, do not spin off entrepreneurial executives in the same way as the telecommunications sector.

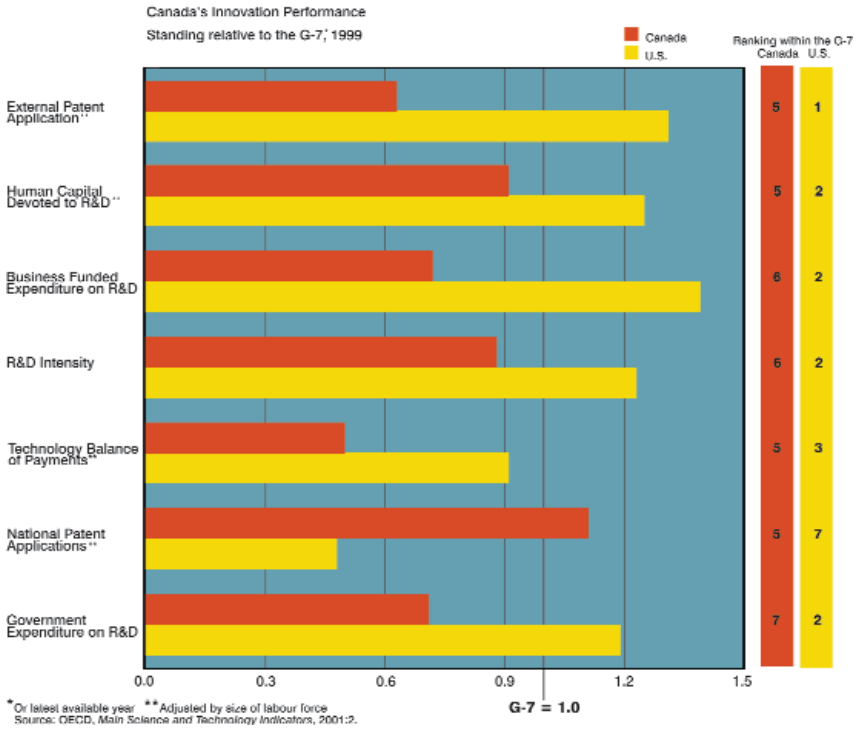
In the past, as detailed previously, there has been considerable support from government to reinforce the scientific skill needed at both the university expert stage and the bench technician stage. *However, there has been little action to develop experienced management*. Quebec implemented a tax infrastructure change for recruitment of senior managers; foreign scientific personnel are exempt from paying part of the provincial personal income tax for five years. This tax holiday is also extended to foreign experts who specialize in the "management or financing of innovation activities, foreign commercialization or transfer of leading technology". In 2004, the Biotechnology Human Resource Council identified a similar human resource gap and undertook to make recommendations and suggest action to address this weakness.[87]

2.7.4 Canada's Innovation Gap

Canada is still not realizing the full potential benefits from its investment in R&D. Measured against other leading countries, Canada has an "innovation gap" when assessed on many of the gauges of innovation. Although Canada develops many opportunities, it fails to capitalize and retain long-term value. Canada's innovation performance is near the bottom of the G-7, due to a continuing innovation gap when measured on the number of external patents, R&D intensity, technology balance of payments, business expenditures on R&D and human capital devoted to R&D. The leading countries invest two- to three-fold more in R&D based on GDP (Figure 13).

[87] "Converging Science and Leadership: The Key to the Future," Canadian Biotechnology Human Resource Study (2004).

Figure 13: Canada's Innovation Gap — Expenditures as Percentage of GDP



Canadian researchers and UILO offices are oriented to innovation and global commercialization, as evidenced by the large number of start-up companies generated. However, there is evidence that they form start-up companies at earlier stages than occurs in the US, due to a gap in funding at the seed level needed to strengthen IP, complete proof-of-principle and assess market potential. Consequently, they have weaker patent and product portfolios and are competitively disadvantaged when they seek risk capital for product development.

Research is the basis upon which all new knowledge is acquired. However, to provide the funding for research without a commensurate emphasis on commercialization of these innovations is unsustainable in the long term. Commercialization generates the money that fuels more innovation, and provides the cash flow for additional research. Where is the return on investment? Commercialization provides opportunities to retain the value-added benefits of jobs, capital and manufacturing, and the chance to reverse the brain drain. It also offers Canadians the opportunity to benefit from innovations first. Government has offered strong support for R&D — it now needs to put in place incentives to encourage and facilitate commercialization of Canadian research in Canada by Canadians.

2.8 Opportunities

2.8.1 The Drug Development Process is Changing

Discovery research is exhausting its potential; its concentration is on the 500 well-known target sites whose IP is poorly protected, resulting in a large number of "me too" products. Thus there has been a limited diversity in the number of disease targets, many of which are undruggable. Moreover, we have had a poor understanding of disease. The allure of genomics is that it would provide

thousands of new targets for use in developing new treatments. Genomics is expected to increase the number of target sites from 500 to 10-20,000. Although researchers have already developed some drugs using rational drug design, this process can be considered rudimentary compared to what is predicted from genomics and proteomics.

Genomics does have its own limitations at present. Like recombinant and monoclonal technologies in the past, genomics has contributed a powerful new tool to drug discovery and development, but like them, it will probably not have a significant impact on the pharmaceutical market for at least 10 years. Ironically, genomics has delivered exactly what the biopharmaceutical industry wanted — many new novel targets — but not the tools with which to understand, validate, and qualify those targets.

It was originally expected that gene expression analysis would be a powerful tool for elucidating gene function (gene expression reflects the amount a gene is turned on or off, based on levels of RNA). Furthermore, researchers expected proteomics, which can characterize the proteins or gene products in a cell, to clarify how genes influence health and disease.

It is now clear that knowing what genes are turned off in a sample provides little insight into what the gene's products are doing. Several limitations remain to be resolved. Proteomics is still a relatively slow throughput technology and cannot yet reveal all the proteins in a sample. Some proteins are difficult to find. Proteomics and gene expression are also hampered by the fact that the easiest RNA or proteins to find are often the most common, considered as "housekeeping" molecules, that are present in many kinds of cells. The housekeeping molecules create a lot of background noise, making it difficult to find the rarer, more important genes being expressed. Furthermore, proteins undergo post-translational modification, which alters their structure.

Two facts must be emphasized about the status of today's medicinal and scientific knowledge. First, on the macro level our knowledge of the body's physiology is good, but second, our knowledge on the micro level (the cellular processes) is still very poor. The cells of the body continuously communicate, regulate and regenerate. Our understanding of the myriad of cellular functions and metabolites is low, because of the difficulty of accessing the cellular environment and the limits of current technology and complexity of the cell.

It is still expected that the new research targets will represent a step forward in the drug discovery paradigm and that several will be breakthroughs. In addition, besides being valuable for target discovery and validation, genomic tools can have a substantial impact on lead optimization and clinical trials. Genomics is providing useful tools such as gene and protein signatures of toxicity, drug response, disease profiling and ways to rule out compounds that may have multiple biological targets.

Gene expression, protein expression and determination of metabolite levels are all emerging as rich sources of prognostic, diagnostic and drug response markers. These markers form the basis of useful products and are used in clinical trials to guide patient selection and/or optimal dosages. Several groups are in the process of assessing the expression of disease targets for diseases, such as cancer, to identify differential characteristics that would predict whether the disease might respond to drug therapy or surgery. Potential markets for the new technologies include diagnostic services, therapeutic agents and tools (DNA sequences, instruments, DNA micro-arrays). Other applications include DNA profiling

(forensics), workplace and environmental monitoring, and clinical trial design, conduct and support.

The current drug development process has served us well, but it is not fit for the future. It is lengthy and expensive because of poor understanding of disease, lack of predictive capability for drug actions, drug toxicology, and the inability to select patients who might benefit. The consequences have been a high attrition rate, treatment of many patients who would not benefit, and observance of adverse events and drug interactions only after its launch.

The potential for the genomic approach to provide many more products personalized to subpopulations creates two issues: first, the sales of such products are expected to be smaller than blockbuster size; second, more products will have to be developed through the expensive clinical phases. Development requires better selection methodology and the evolution of clinical testing procedures to handle larger numbers at lower cost.

The FDA has addressed this issue in a March 2004 document[88] titled "Innovation or Stagnation". It announced a plan for the modernization of drug development and biomedical technologies. The document states that:

Underlying everything, one finding: our development tools are decades behind in relation to our needs. Our *in vitro* and animal techniques can no longer keep up with the complexity of the targets being selected and are inadequate in their prediction failures. Even the advances in functional genomics and in proteomics, which provided us with the required targets and paths of molecular action, do not yield the systemic vision necessary for predicting the effects on the entire cell, organ or organism.

A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.

An intense scientific effort must be undertaken in order to modernize the development of new therapies. This involves shifting the work in toxicological testing upstream from clinical trials, and predicting much earlier, and at lower cost, possible problems of toxicity and lack of efficacy in new molecular entities. In the future, large-scale confirmatory clinical trials may be replaced with conditional approvals and ongoing testing. The main tools involved are proteomics and toxicogenomics, predictive toxicology *in silico*, the use of human cell lines to predict toxicity, the redefinition of clinical effectiveness objectives with the help of biomarkers for the disease, and computer design of model systems.

The situation therefore provides opportunities for those involved in the design of methods applied to the development of drugs. Work continues on the new targets, but also on the development of a new science for the efficient development of those candidates.

[88] US Food and Drug Administration, Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products (March 2004), www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf

2.8.2 The Delivery of Health Care Will Change

We should expect to see a shift in the delivery of health care from the traditional medical evaluation model consisting of identification of a symptom, medical history, diagnostic testing assessment and drug treatment plan. The model of the future will involve maintenance of a health profile, assessment of genetic, environmental and lifestyle health risks and use of a multi-year health plan integrated with patient databases.

Pharmacogenomics will shape the health care business. The emerging potential to treat subpopulations of patients with more effective therapeutics requires the integration of drugs into prognostics and diagnostics; first to identify the most appropriate patients and then to monitor their treatment. Increased patient specificity for these drugs will concentrate diagnosis and treatment in small numbers of specialists within R&D facilities.

This requirement creates new opportunities for the Canadian biopharmaceutical industry, because Canada's integrated health care system brings together the specialist knowledge of patient characterization maintained in databases with the industry's selective treatments. Coupled with a disintegration of the big pharma structure, this enables numerous biopharmaceutical companies to find a strong niche.

2.8.3 Restructuring of the Biopharmaceutical Industry — A New Emerging Value Chain

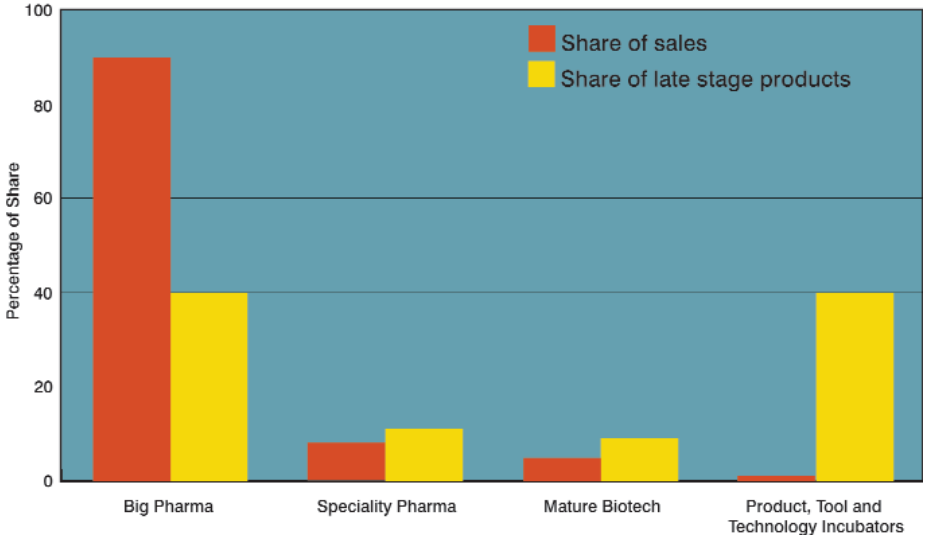
The new technologies will lead to a restructuring of the biopharmaceutical industry and opportunities for its expansion. They are permitting a paradigm shift, expected to occur in the discovery and development of drugs and the delivery of health care.

The "big pharma" value chain model will change. Worldwide, the large integrated pharmaceutical companies have dominated the industry, including new product development. Since Canada lacks an indigenous large pharmaceutical company with worldwide presence, it has traditionally been difficult to break in.

Today, however, big pharma is facing several difficulties, ranging from weak product pipelines, patent expirations, generic competition, and expensive promotional practices and pricing challenges. Investors expect annual growth from big pharma of 12-15%. To achieve this, its value chain model has depended upon large research expenditures to produce the blockbuster drugs needed to sustain sales volumes and share price. Size has been used to create barriers to entry, but big pharma cannot produce the number of new blockbusters needed to maintain growth.

Big pharma is caught in a technology lag. Its historical success was based on exploiting about 500 out of 1,200 targets. However, the increase in available targets provided by genomics has not led to a proportional increase in new products, resulting in a decline in product output. Already innovation is shifting away from big pharma towards biotech companies. The former now accounts for less than 50% of both new late-stage products in the industry pipeline and NME (new molecular entities) product introductions as shown in Figure 14.

Figure 14: Share of New Products between Pharma and Biotechnology



Source: B.G. James, "Big Pharma: The Beginning of the End or the End of the Beginning?," Pharmaceutical Industry Dynamics, Decision Resources, May 5, 2003.

Faced with these pressures, big pharma is restructuring its integrated value chain model, which provides new opportunities to expand the Canadian biopharmaceutical industry. Already, since the easy research has been done, big pharma is increasing its reliance on universities for research, as they have the skills to address the growing complexity of treatment.

In addition, big firms are forming alliances with smaller biotechnology companies to gain access to new opportunities. In the future, biopharmaceutical companies will be small, faster, leaner and interrelated. Big pharma will maintain a core of activities but outsource research, clinical trials and product development. Consequently, building an industry of smaller, more specialized, faster moving companies will be the value model, rather than the traditional approach of developing an integrated worldwide company. This new model offers a bright future to the Canadian industry, but to capitalize on this opportunity, the current weaknesses must be overcome.

2.9 Canada's Technology Transfer Process: Source of Commercialization Weakness

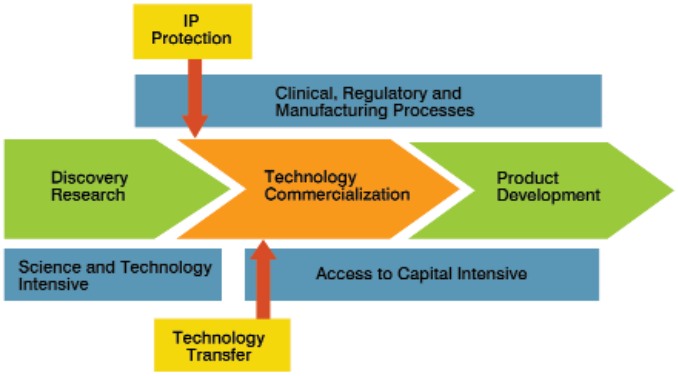
Technology transfer describes a formal transfer of rights to use and commercialize new discoveries and innovations resulting from scientific research to another party. Universities typically transfer technology by protecting, then licensing innovations. The major steps in this process include the disclosure and patenting of the innovation, concurrent with publication of research and licensing the rights to innovations to industry for commercial development.

2.9.1 Effective Technology Transfer

In order to capitalize on the new opportunities arising from the increasing investments in research, technology transfer from universities to commercial development must be timely and efficient. This includes protecting and strengthening patents and IP, testing proof-of-principle and assessing the

market. The transfer process might result in new start-up companies or simply out-licensing, but the research entity must have adequately protected its discoveries through patents and know-how to justify commercialization. The TRM analysis revealed *the imperative need to improve IP protection and strengthen technology transfer*.

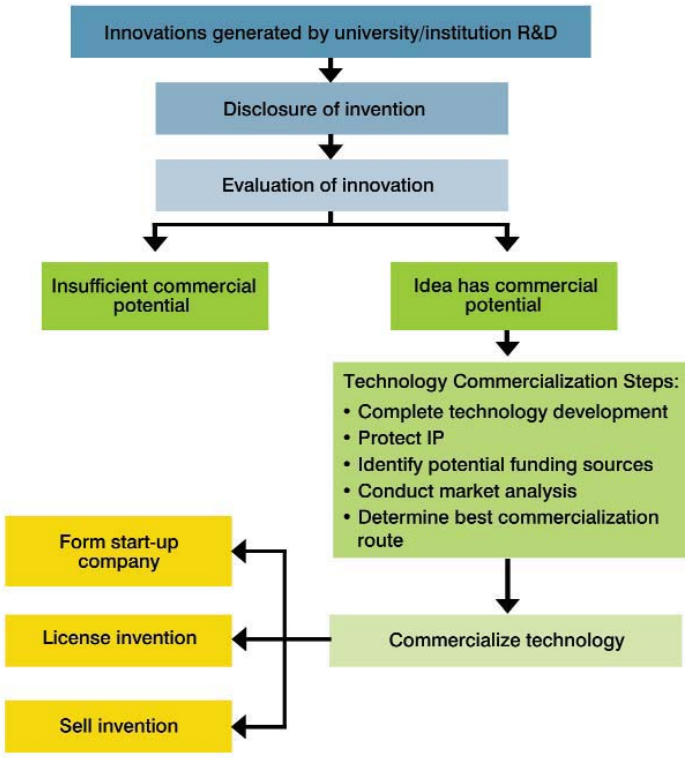
Figure 15: Technology Commercialization — Technology Transfer and IP Protection



Source: TRM Steering Committee.

This process also coincides with the formation of new companies to establish the organizational culture for commercialization and to ensure a focus on product development. While research discovery is S&T intensive, product development is capital intensive (Figures 15 and 16).

Figure 16: The Steps of Technology Commercialization



Source: TRM Steering Committee.

Canada relies more than any other country on its universities to undertake research and initiate innovation of new discoveries in biopharmaceuticals. Universities are also the locus of most start-up companies and the transfer of technology to the commercial sector. Despite low levels of R&D funding in Canadian universities, compared with that of leading OECD economies, we have seen that Canadian researchers are very effective at producing high numbers and quality of scientific citations and discoveries.

The analysis presented below indicates that researchers and UILOs are highly oriented to identify opportunities and to transfer the technology for commercial development. They have been very active in starting new companies, forming proportionately twice as many as in the US. Canadian universities are as productive as those in the US on most measures per dollar of research spent, but they achieve lower licensing revenues and are issued fewer US patents.

Table 21: Comparison of Technology Transfer of Canadian and US Universities, 1999-2003

New start-up companies	Canadians created 2.5 times more spin-off companies per dollar spent on research.
Invention disclosures	Canadians disclosed as many inventions per dollar spent and executed as many licences per $1M spent.
Patents	Canadians succeeded in having only half as many patents issued per $1M spent.
Licensing	Canadians were equally successful in licensing inventions; however, they generated only half the licence revenues.

Source: TRM Steering Committee.

Taken together, these results suggest that new companies are started prematurely, before they have had a chance to sufficiently develop or protect high quality IP. The impact is that fewer patents are issued, and those that are issued may not be sufficiently strong. Premature company start-ups lead to weaker companies with poorer IP protection, resulting in lower license values and greater difficulty in obtaining risk capital for development than would be the case after a longer period of incubation.

The federal Advisory Council on Science and Technology (ACST) noted that:[89]

... Canadian universities are well placed to strengthen Canada's innovative capacity and productivity performance. They are positioned to play a more prominent role in fuelling national economic growth and social development than universities in most other G-7 countries, including the US universities.

However, the ACST also warned that Canadian universities are far less effective in generating economic benefits than their US counterparts.

[89] "Public Investments in University Research: Reaping the Benefits," ACST (1999).

Canada's technology transfer from drug discovery to drug development and commercialization has been assessed according to several criteria. They include:

- growth in number of start-up companies;
- number of disclosures of invention and number and quality of patents issued;
- licences and options executed;
- licensing income received.

2.9.2 Growth in Number of Firms

As shown in Table 18, the number of biotech companies increased by 208 from 1997 to 2003, significant, as when compared with the US industry (Table 22), Canada forms twice many start-ups (per $1M of research).

Table 22: Canadian Invention Disclosures, Licensing, Patents and Start-Ups Compared with US (Normalized Measure)

Universities	Invention Disclosures Received per $1M	Licences & Options Executed per $1M	Licence Income Received per $1M	US Patents Issued per $1M	Start-ups Formed per $1M
Canada-all 19 Universities	0.539	0.190	$25,270	0.095	0.040
US Top 19	0.638	0.190	$50,300	0.202	0.019
US All 168	0.624	0.185	$51,579	0.177	0.021

Source: Association of University Technology Managers, Technology Transfer at Canadian Universities: Fiscal Year 2001 Update (May 2003).

2.9.3 Survival of Start-Ups

An assessment of companies spun out of universities from 1995 to 2001 was estimated from a sample of data reported from nine Canadian universities active in technology transfer. Biotech spin-offs account for about 52% of the companies created, of which about 70% survived until 2003.[90] This is reasonably good, but most of these survivors are small, residing in university settings and not advancing to later stages of development.

2.9.4 Invention Disclosures, Licences and Licensing Revenue

Canadian researchers and universities appear to be as efficient as their US counterparts in terms of the number of invention disclosures and licences executed per $1M. However, Canadian universities receive only half the revenues that their US counterparts derive from licensing deals. Furthermore, the studies

[90] B.P. Clayman and J.A. Holbrook, The Survival of University Spin-offs and Their Relevance to Regional Development (2004). Centre for Policy Research on Science and Technology (CPROST), Simon Fraser University, 515 West Hastings Street, Vancouver, B.C. V6B 5K3 Canada. See also www.sfu.ca/cprost/docs/CFI%20spinoffs%20March2.doc

indicate that the amount of technology transferred is roughly a linear function of research expenditures.[91]

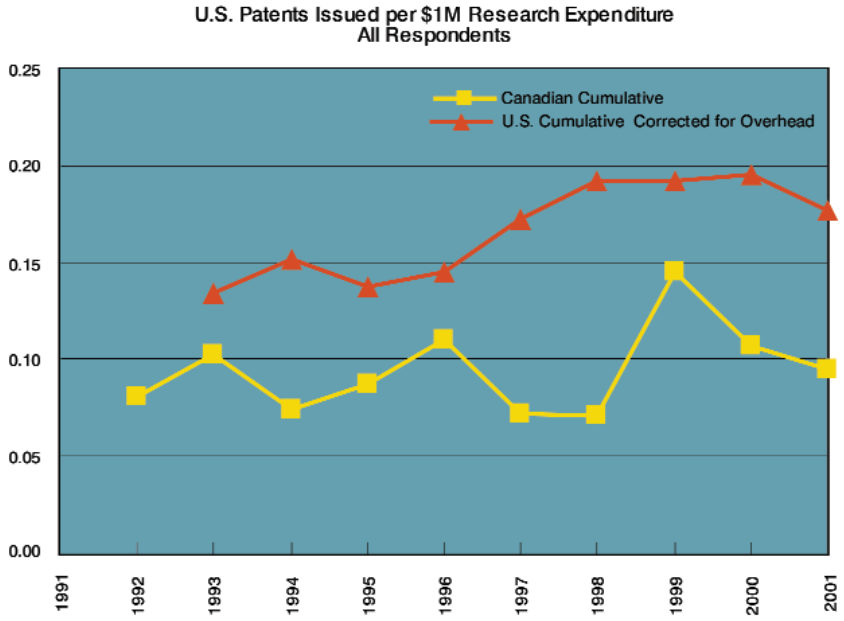
2.9.5 Patents

Generally, although Canadian universities are almost as efficient as their US counterparts in invention disclosures, they are only able to receive half as many patents per $1M invested (Figure 17 and Table 22). US universities exceed Canadian output in patents issued by two fold.

The issuance of patents in the US is significant because most new technology must usually receive US protection (in the largest market in the world) for commercial success. Canada's revenue shortfall could relate to Canadian applications for patents being weaker, less significant or too late compared to US applications. In any case, it would reflect lower IP protection that could have a negative impact on the evaluation of a company's product portfolio when seeking development funding.

This assessment is reinforced by data concerning patent citations presented above (section 1.5.4 Patent Performance). Patent citations provide a measure of the importance of the underlying invention with more frequently cited patents tending to be more important. The share of citations for Canadian patents was smaller than the share of counts, which suggests that Canada's patents were on average less important.

Figure 17: US Patents Issued per $1M in R&D Spent



Source: Association of University Technology Managers, Technology Transfer at Canadian Universities: Fiscal Year 2001 Update (May 2003).

[91] Association of University Technology Managers, Technology Transfer at Canadian Universities: Fiscal Year 2001 Update (May 2003).

Another assessment of Canada's patent strength is provided by data from the European Patent Office for the period 1987 through to 1997. The data provide the share of each country's number of biotechnology and pharmaceutical patents filed as well as patent citations. While patenting is a broad indicator of technological activity, patent citations provide a measure of the importance of the underlying invention — widely cited patents tend to be seminal patents. The share of citations for Canadian patents was smaller than the share of counts, which suggests that Canada's patents (to 1997) may have been on average relatively less important than those of its major competitors. Alternatively, there was perhaps comparatively little activity in technologies such as genomics, combinatorial chemistry, antisense, therapeutic monoclonal antibodies, and gene therapy.

A similar conclusion was reached by Science-Metrix[92] for patents at the USPTO from 1990-2001. Canada ranked fifth in terms of number of patents and eighth in patent citations; in addition, its average citation per patent was below the average.

2.10 Does Canadian University Start-up Strategy Weaken Commercialization?

Two conclusions flow from the previous data. First, universities are following a strategy that emphasizes forming start-up companies and forgoing the early financial returns from licensing the technology in favour of building equity investment in the start-up companies. Canadian universities are more dependent on new company formation as a strategy than those in the US because they lack both financial support from pharma companies, and a critical mass of Canadian-owned research-based pharmaceutical companies to act as receptors. In either case, strong IP is a prerequisite for obtaining funding from venture capital, licences, or strategic alliances. Failure to successfully commercialize innovations is due to lack of risk capital investment to develop each company.

Second, the incentive to create new companies, undertaken by universities to meet national goals, leads to start-ups being launched prematurely, before demonstrating real commercial value and without regard to sustainability. Implications of this hypothesis are that the companies would have weaker or irrelevant patent protection, deterring investors from providing risk capital and thus limiting their commercial development. These companies would benefit from being nurtured longer within universities.

BioQuebec recently concluded in a study that Quebec biotechnology companies are started prematurely, giving rise to many ventures whose technological maturity is weak. The study showed that Quebec companies tend to start at earlier developmental stages than do those in the US. The report also echoed the findings summarized above, namely that Quebec start-ups achieve fewer patents and licensing revenue (Table 23).

[92] Biopharmaceuticals in Canada—Benchmarking of Canadian Biopharmaceutical Science and Technology, internal study prepared for Industry Canada (March 2003).

Table 23: Measures of Technology Transfer in Quebec Universities

	Inventions Disclosed/ M$ R&D (%)	Patent Applications/ Invention (%)	Licences/ $ Research (%)
Quebec	29.1	66.4	2.19
Canada	27.8	60.1	1.59
US	30.1	85.4	3.27

Source: SECOR Consulting, From Research to Marketing: Conditions for the Maturation of University Research in the Life Sciences, report to BioQuebec, February 2005.

Like Canada, the UK has a relatively low GERD/GDP ratio and a government that has taken steps to improve commercial performance. The UK also has a strategy that emphasizes start-ups even more strongly than Canada. A recent review in that country showed that the University Challenge Funds set up in 1999 to provide proof-of-principle and seed financing were predominantly used instead for early-stage investment in spin-offs, suggesting that these funds have been one of the main drivers of spin-off activity.

Canada's poorer patent performance may be due to having fewer personnel with IP experience in UILOs, which have been established for shorter periods of time compared with the US. A recent analysis by the Association of University Technology Managers on the full-time equivalent (FTE) personnel devoted to commercialization activities found that all Canadian regions had more FTEs (normalized to research expenditures) than US sites.[93] However, Industry Canada reports that US universities and hospitals devote more resources to their technology transfer offices and to the management of IP than their Canadian counterparts. In 1999, for example, there were 34 full-time technology transfer employees in 10 Ontario universities, compared with 141 in 11 California institutions. Technology transfer in Canada can be strengthened by consolidating smaller offices, a small levy on government grants to recruit or train tech transfer personnel, or a special university targeted program such as implemented in the UK. CIHR recently established an IP management program to provide institutions with up to $200,000 in annual funding to explore the commercial potential of their discoveries, including training and technology assessment.

2.11 National Strategy is the Issue, not Government Funding

It is the contention in this report that companies are started prematurely because universities, the site of most discovery and innovation in Canada, are encouraged to use the number of companies launched as a measure of success. Many of these companies have had insufficient time to protect IP and confirm proof-of-principle, essential for development.

This has consequences: VC start-up financing is used for IP protection rather than for product development, and having a larger number of companies means the available risk capital must be spread over more investments. A further impact is that due to weaker patent positions, follow-on financing by

[93] Dr. Chris Riddle, Commercialization Strategies of Canadian Universities and Colleges, Advisory Council on Science and Technology (March 2004). For a comprehensive study of university licensing practices in biotechnology, see Mark G. Edwards, Fiona Murray & Robert Yu, "Value Creation and Sharing among Universities, Biotechnology and Pharma", Nature Biotechnology, 21, (June 6, 2003) pp. 618-622. For data on licensing trends, especially the value difference between early- and late-stage agreements, see Recap website (www.recap.com).

venture capitalists, on equity markets or via strategic alliances, dries up when the more sophisticated investors identify the weaker competitive position of the companies. Emphasizing early company launches does not guarantee high-quality companies, and only such companies will be successful in obtaining financing in Canada and can choose financing in the larger US market.

As reviewed earlier, Canada funds the biotechnology sector at a high proportion of its national science budget compared to other OECD countries and the US (although less well as a percentage of GDP). Most of these funds are allocated to discovery research. In addition, business is the dominant provider of funds for product development in all countries, but Canadian business (from VCs, equity, alliances) invests at a rate of only about 75-80% of that in the comparative countries. Conversely, Canadian venture capitalists do invest proportionally as much in Canadian biopharma as their American counterparts invest in US companies.

Clearly, a change in strategy — allocating resources to addressing commercialization weaknesses early — would lead to stronger and fewer companies better able to justify later investments in development. These companies would then offer less risk for investment with later-stage VC, equity and strategic alliance financing.

However, Canada's commercialization problems are more fundamental than simply encouraging premature company start-ups. In today's more competitive climate, it is becoming clearer to industry participants that while these individual elements are useful and still significant, the real problems exist at the national level. Under the current approach, the interactions of the various elements are generating unique Canadian barriers to development of biopharma companies. Essentially, the argument in this report about commercialization is this:

Canadian programs for this industry need to rebalance the focus from creating new companies in the direction of ensuring that new companies are sufficiently well-incubated that when they are released into public markets, they are robust enough to survive. This implies not just a rebalancing in allocations from early- to late-stage company development, but rather a rethinking of the way companies progress through all stages, with an emphasis on reinforcing durability and sustainability.

Participants in TRM consultations and surveys identified two stages of development where access to risk capital is deficient and chokes off the growth of Canadian companies. The first phase is the shortage of seed/pre-seed to start-up stage funding. This is the period of establishing proof-of-principle, strengthening IP, marketing assessment, business planning and initial product prototyping. As a result, start-ups have insufficient funds to properly protect IP and later-stage companies are forced to develop only a lead product. A related problem: venture capitalists also request that companies develop only one lead product, minimizing the amount of investment per company. Entrepreneurs play along in order to reduce their dilution. The losers are the companies that have to develop in slow gear and take excessive risk, whereas a multiple-product strategy would create more value, more rapidly.

This one-product strategy results in a lower probability of success and lack of development of other products. In contrast, later-stage companies (usually stage III) with the potential for near-term revenues are not identified as lacking capital, except perhaps to establish manufacturing. Such companies are

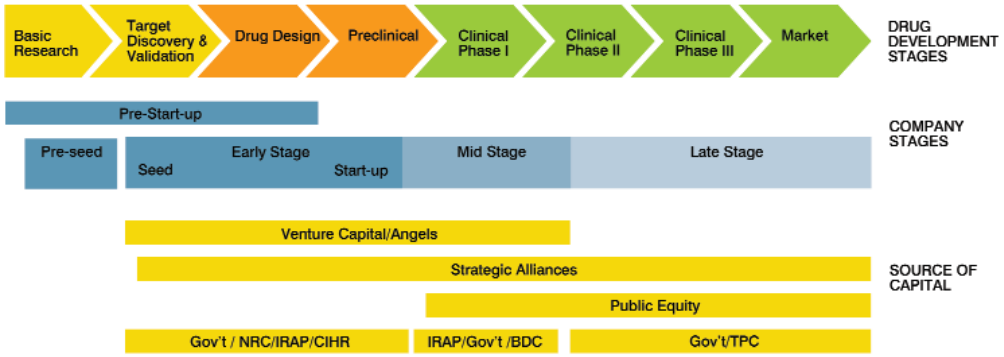
relatively rare, however. The bottom line: for most CEOs consulted in the TRM process, biopharmaceutical companies are very small; many receive only seed or angel money, and continue to operate within government or educational institutions. Their ability to grow is limited and the turnover in such firms from year to year is substantial.

2.11.1 Sources of Capital

Biotechnology companies use several sources of financing, depending on their development stage (Figure 18):

- private capital from angels and VC funds;
- public equity from IPOs and follow-on financing;
- strategic alliances with big pharma and other biopharmaceutical companies;
- government grants, contributions, and R&D refundable tax credits.

Figure 18: Sources of Capital relative to Product Development and Company Stage



Source: TRM Steering Committee.

Government grants are used primarily in the research and discovery phase. In the seed and start-up phase, government grants, angel funds and VC investments dominate. Venture capitalists tend to favour early-stage companies from start-up on to the end of mid stage, when they expect equity placements to provide them with a return. Equity typically is sought by late stage and mid stage companies near late stage to obtain funds for the more expensive late development or for multiple products. Strategic alliances are a critical source of capital at all stages. Some companies attempt to follow a development strategy of retaining ownership until the late stage in order to retain a larger share of marketing revenue. Others, by design or need, out-license or enter collaborations earlier in order to complete development, and accept a lower return.

2.11.2 Benchmarking Financing Activity vs US and Other Countries

Capital structure explains the situation. Data for Canadian sources of funding are incomplete, especially for capital obtained through strategic alliances and private equity in public companies. The US data are more complete. The tables below show how crucial (at 39%) are venture capital and angel investors for Canadian firms; alliances supply only 12% of total financing. In the US, the picture is reversed: venture capital accounts for 10% of total industry financing and alliances 32.9%. Public markets account for 52% in Canada and 48% in the US. The heavy reliance of Canadian firms on VC funding virtually dictates as rapid as possible a launch into public markets.

Table 24: Sources of Funds for Canadian Biopharmaceutical Companies ($CM)

	C$M Invested In Life Sciences						
	1999	2000	2001	2002	2003	2004	Total
Venture Capital/Angels*	440	826	651	479	408	466	3,270
(#)	(136)	(258)	(190)	(185)	(164)	(144)	
Avg./financing	3.2	3.2	3.4	2.6	2.5	3.2	
Public Equity—IPOs**	43	152	30	16	0	38	279
(#)	(7)	(11)	(5)	(2)	(0)	(2)	(27)
Avg./financing	6	26	6	8	0	19	10
Public Equity—Secondary Financing***	776	925	514[1]	318	1,345	566	4,236
(#)	(30)	(57)	(27)				
Avg./financing	26	16	19				
Strategic Alliances+	NA	67.2	188.3	347.9	151.4	252.2	1,007
Total	**1,259**	**1,970**	**1,383**	**953**	**1,904**	**1,322**	**8,792**

** Source: Where Does Biotech Fit? 2004. Trends in Biotech Investing in a Slimmed Down Venture Capital Market, MacDonald and Associates Ltd. www.canadavc.com/files/public/BioContactQuebecOct604.pdf*
*** Source: Survey of IPOs in Canada in 2004–1999. PriceWaterhouseCoopers. Price Waterhouse IPO Survey. www.pwc.com/extweb/pwcpublications.nsf/docid/E2BCAED8E453FBA1852570CA00178D65*
**** Source: Beyond Borders. The Global Biotechnology Report. Ernst & Young, June 2005, 2004, 2003, 2002. www.ey.com/global/content.nsf/International/Biotechnology_Report_2005_Beyond_Borders*
1. In addition, there was a financing of Biovail in the sum of $934M.
+ Canadian Biopharmaceutical Alliances, Life Sciences Branch, Industry Canada, February 2005.

2.11.3 Venture Capital

In addition to capital structure, size also plays a significant role in determining company strategy. The average VC and IPO deal sizes are significantly lower in Canada, and fewer funds are flowing to more companies. Financing rounds in Canada are substantially smaller than those in the US (Table 25), reflecting differences in the size of the capital markets, the maturity of the industry, and a greater risk profile for investors. In the US, IPO candidates typically have products in Phase II or later, whereas proof-of-principle for a Canadian firm is often not established before it goes public. One consequence of insufficient capital is that companies do not have the resources to develop in parallel multiple products. As a result, they concentrate on a single lead product. As discussed earlier, the disadvantage of this is that the probability of failure is higher and the time for development is longer. A company with a technology platform that can generate multiple products or opportunities rather than rely on solely a lead product, which has a high risk of failure, offers additional value to investors. Such a strategy increases the probability of success.

Size matters in other ways, too. Canada has one of the highest levels of VC investment as a share of GDP among OECD countries. Moreover, the Canadian VC market invests proportionally (on a 10:1 ratio) similar amounts of funds as the US market for all types of VC investments. For the last few

years, Canadian venture capitalists have invested the same proportion of total funds in the life sciences but funded proportionally more Canadian companies than those in the US (Table 26).

Table 25: Average Deal Sizes Canada vs US

	Canada ($US)	USA($US)
Venture Capital — Average Deal Size	$2.4-4M	$12-14M
IPO — Average Deal Size	$5-14M	$50-100M

Source: MacDonald & Associates Ltd., Where Does Biotech Fit? (2004).

As a result, the average deal size in Canada is about one third that in the US, at $2.5-4M compared with $12-14M in the US.[94] Two consequences follow: (i) with a larger number of smaller companies per capita than the US, each company funded tends to receive a smaller share; and (ii) the under-capitalized companies are too small to attract much attention from the richer, more diverse capital markets to the south. The small size of the deals in effect confines the opportunity to the smaller Canadian market. However, a Canadian company with sufficient strength and promise, and a global perspective, can seek capital in the larger US market, as many have done.

Table 26: Biotechnology Industry Fundraising in US & Canada (US$M)

	2000		2001		2002		2003		2004	
	Can[2]	US[1]	Can[2]	US[1]	Can[2]	US[1]	Can[2]	US[1]	Can[2]	US[1]
Public Companies										
IPO	104	6,485	16	440	10	445	0	453	85	1,701
Average/IPO	17	103	4	52	5	52	0	65	42	59
Follow-on	674	12,651	910	2,539	318	979	1,139	3,536	435	3,388
Average/financing	15	202	12	61	62	45		82		79
PIPEs	N/A	4,061	N/A	1,741	N/A	1,007	N/A	2,051	N/A	2,417
Debt Convertible	N/A	5,728	N/A	4,848	N/A	5,251	N/A	7,171	N/A	8,418
Private Companies										
Venture Capital	481	2,872	388	2,397	199	2,688	206	2,841	271	3,733
Average/financing	3	13	2	11	2	10	3	14	3.8	17
Other offerings		203		9		178		294		269
Total Financing	1,259	32,000	1,314	11,974	527	10,548	1,345	16,346	791	19,926
Alliances (Partnering)[1,3]	67	6,901	188	7,486	348	7,496	151	8,933	252	10,933
Total	1,326	38,901	1,502	19,460	875	18,044	1,496	25,279	1,043	30,859
Market Capitalization	16B	353B	13B	255B	9B	224B	14B	344B	14B	466B

Sources:
1. Biotech 2005, Industry Review and Outlook, Burrill & Company, October 2005. www.burrillandco.com/pdfs/gsb_laguna_2005.pdf
2. Beyond Borders, The Global Biotechnology Report, Ernst & Young, June 2005–2002. www.ey.com/global/content.nsf/International/Biotechnology_Report_2005_Beyond_Borders
3. Canadian Biopharmaceutical Alliances, Industry Canada, February 2005.

[94] MacDonald & Associates Ltd., Where Does Biotech Fit? (2004).

2.11.4 Seed Stage Firms

Seed stage firms and those seeking $1M or less have a difficult time attracting venture capital because high transaction costs and return targets make small projects uneconomical. IRAP and angel investors tend to invest much more in start-ups than VC firms, but IRAP is often oversubscribed while angels are difficult to find. Tax incentives and the treatment of capital gains have traditionally been used to encourage more angel capital. A rollover provision allows Canadian investors to defer capital gains taxes from one investment if the proceeds are invested in another qualifying business, but the120-day reinvestment period may not provide sufficient time to find and assess another opportunity and the losses available for write-off are not as generous as in the US. The US has a far larger number of wealthy individuals along with investment clubs that serve as networks for business angels.

Venture capital above $10M is also difficult to arrange, forcing Canadian firms to go public sooner than those in the US. This results in an industry predominantly populated by small cap firms with poor trading liquidity and higher risk profiles. US venture funds are substantially larger — a typical US fund might close at $75M to $200M — allowing them to support larger deals because they can tap into pension funds and charitable foundations. However, these sources of capital play a much less active role in Canada. Recent tax changes eliminated the 30% ownership ceiling in limited partnerships (such partnerships were previously treated as investments in foreign property), which should make it easier for Canadian pension funds to put money into venture funds.

The Business Development Bank received an extra $250M over five years (2004) to support biotechnology and other innovative Canadian companies, but the average deal size is expected to be less than $5M, so it will primarily cater to early-stage biotechnology companies rather than those in Phase II or later that require $10M or more.

2.11.5 Public Equity

When Canadian biotechnology firms access the public equity markets, few have deep product pipelines or products in late-stage development, so their value tends to be pegged lower than that of US firms. Over 80% have a market capitalization of less than $100M (US firms of a similar size would be venture backed instead), and lack the trading liquidity required to get the attention of US analysts or large institutional investors (the buying and selling of large blocks of shares would affect the share price and force fund managers to assume control). After their IPO, secondary offerings are relatively scarce in Canada because of the lack of a large liquid retail market for biotech stocks. Private placements have been much more popular, due to quicker access to cash and reduction in the time and expenses for investor road shows. Biotech companies, expecting to obtain equity capital, must cope with the cyclical nature of the stock market and obtain financing during certain financing windows. In the last 15 years there have been approximately four such financing windows — around 1991, 1996, 2000 and possibly 2004-2005; periods of investor favour dependent on rising stock prices that lead to an increased demand for IPOs and follow-on offerings. This in turn influences VC activity both in disbursements and in fund raising because of the likelihood of a successful exit. The cyclical nature of the markets has made access to capital as much an issue of timing as of pipeline success.

Like other high technology sectors, the biotechnology industry rode the stock market bubble in 2000, but the subsequent dramatic decline in stock prices closed the window for public offerings. For example, in 2001, only 50% of small biotechnology firms seeking capital were able to reach their financing targets, compared with 80% of medium-sized and 66% of large companies. Only the larger firms were successful in raising any significant amount of money, and then primarily through alternate financial instruments such as draw-downs on equity lines of credit, private placements with institutional investors, convertible debt offerings, and PIPEs (private investment in public equities).

Public companies generate most of their cash in down markets by turning to private sources (convertible debt, PIPEs). The cash position for the vast majority deteriorated sharply, forcing the industry to shift into survival mode — dropping projects and reducing staff. With an IPO exit closed, VC firms are forced to carry their existing investments longer, leading to a cutback in new deal activity. For those successful in attracting venture capital, the decline in stock prices affected private company valuations, causing entrepreneurs to give up more equity than during the market peak.

In periods of market downturn, biopharmaceutical companies must survive by having or conserving sufficient cash to ride out the cycle. Clearly, those companies with products closer to the market and with stronger patent and product portfolios will be more successful and enduring.

2.11.6 Strategic Alliances

Compared with the US, Canada fares poorly in the number and value of strategic alliances between firms. As shown in Table 24 earlier, strategic alliances (partnering) are the largest single source of capital for US companies. This reflects the aforementioned innovation gap and the relative lack of large domestic pharmaceutical companies in Canada. Most Canadian biotechnology companies are newer and smaller than those in the US biotechnology sector. Canadian companies are increasing the number and value of global alliances, but are still not at the same level proportionately as our major trading partner, although according to one observer Canadian firms are now ahead of Denmark, France, Sweden, Switzerland and Australia.[95]

Despite the growth in number of alliances, the value problem remains. This was underlined by participants in the TRM consultation, who generally estimated that compared with their US counterparts, Canadian companies tended to have single or minimal alliances and to focus on only one disease indication, whereas US companies have multiple alliances and are developing multiple disease indications. This reflects the fact that Canadian company alliances are generally early-stage alliances, while those of US companies come later in the development process.

Partnering is an essential element of company development. Most biotechnology companies have no marketed products (often-quoted revenues consist mainly of interest income from invested capital and income earned from alliances and R&D tax credits) and lack the resources to exploit the products they are developing. Strategic alliances can provide Canadian biopharmaceutical companies with additional

[95] Bruce Rassmusen, Alliance Opportunities for Australian Biotechnology, Pharmaceutical Industry Project Working Paper Series, No. 23, Centre for Strategic Economic Studies, Victoria University of Technology, Melbourne Australia (2004), p. 6, fig. 3, citing Recap data.

capital, expertise in product development, access to other technologies, and market access or manufacturing capability. They also provide a company with validation of its technology or the technology platform by a party experienced and knowledgeable in the field. This external validation enhances a company's access to equity market and private capital. Strategic alliances are increasingly important avenues of access to new products and technology for big pharmaceutical companies desperately searching for innovative products to fill their depleting product pipelines. Biotech companies have also been increasing their alliances with other biotech companies, rising from about 27% to about 55% of all alliances.

Alliances are usually structured as out-licensing (where the partner takes over the expense and expertise of development) or co-development deals. Pre-commercial payments over the life of an alliance typically combine up-front licensing fees (cash and usually equity purchases), R&D remuneration, milestone payments geared to technical and regulatory accomplishments, and royalty payments for successful marketing of a drug. In 2004, these ranged from an average of US$73M for contracts signed at the early stage (discovery and lead) to US$82M for late-stage (Phases II and III) projects.

Because agreements are primarily structured towards milestones, most of the risk is borne by the biotechnology company, which will only collect the full amount if all milestone targets are met and the project proceeds to conclusion. Over half of alliances are renegotiated or cancelled prior to project completion and only 10% meet the expectations of pharmaceutical executives.

The biotechnology industry predominantly consists of royalty-based companies. Few have the ability or resources to manufacture or market their own products. The royalty rate negotiated depends on a number of factors: inherent risk, availability of competitive technologies, size of up-front payments, any sharing of clinical trial costs, extent of territorial rights granted, therapeutic field of use, whether manufacturing rights are included, and royalty stacking (any sharing of third-party royalties such as drug delivery).

Big pharma has tended to establish most alliances at a very early stage (consequently most of the commercial benefits (profits) flow to big pharma. The earlier a collaborative partner becomes involved the lower the returns, because of the greater risk that the product will never reach the market and the greater investment required by the partner. With the emergence of contract research organizations (CROs), however, the biotechnology industry is now not as dependent on big pharma for clinical expertise. By advancing products further down the pipeline, a firm will not only derive higher royalty rates, but may also be rewarded with a higher market valuation, allowing it to raise more cash with less dilution. To obtain sufficient capital, the strategy of many biotech companies is to take a product through to Phase II trials, to show proof-of-principle, and then find a partner to conduct the more comprehensive Phase III studies. The attempt is to retain ownership as long as possible to enhance future returns. However, with limited capital many companies cannot afford the expensive CRO costs and do not develop all opportunities.

2.11.7 Government Support

To a large extent, the biopharmaceutical industry has always had to struggle for adequate financing. Earlier reports about the industry identified financing, availability of qualified human resources and

the regulatory climate as the principal obstacles to better commercialization performance.[96] In response, governments have put in place a number of measures to help companies move their product development forward. The menu of federal programs available to help biopharmaceutical companies together with current funding is summarized below (Table 27).[97]

Table 27: Government Programs to Assist Biopharmaceutical Companies, by Development Stage

Program	Funding Goals	Investment	Budget
Proof-of-Principle Stage			
CIHR Proof-of-Principle	Demonstrate scientific rationale to commercial application	$100K	$22M
CIHR Proof-of-Principle Partnered	Same	$100K + $200K partner	
NRC IRAP	New or improved products	To $350K	$30M
NSERC Idea to Innovation	Proof-of-principle and tech transfer		$48M
CIHR IP Management Program	Accelerate the transfer of knowledge and technology residing in universities and hospitals. Grants are intended to strengthen the ability to manage IP, to attract potential users and to promote the professional development of IP personnel.		
Early Stage			
IRAP-TPC (Technology Partnerships Canada or its equivalent successor)	Invests in R&D in knowledge-based sectors	Up to $500K as loans	
Business Development Bank of Canada	Boost VC access		$50M fund-of-funds
CIHR/R&D Clinical Trials Program	Partner support for clinical trial development		
Scientific Research and Expense Deduction tax credit	Provide tax credits for R&D expenses		$462M in annual tax credits given
Mid Stage			
BDC VC Investments	Boost VC investment		$40M annually
Technology Partnerships Canada	Invests in R&D in knowledge-based sectors		$25M annually
SR and ED tax credit	Provide tax credits for R&D expenses		
Late Stage			
Technology Partnerships Canada or its successor	Invest in R&D in knowledge-based sectors	$1.5 to $80M	$350M all sectors

Source: TRM Steering Committee.

[96] See, for example, Leading in the Next Millennium, National Biotechnology Advisory Committee, Sixth Report, 1998, particularly Chapter Two and Appendix 1, Recommendations.

[97] Kathryn Howard, Director General, Life Sciences Branch, Industry Canada, Presentation to BioteCanada Conference 2003: Adapting to the Times (May 29, 2003), slides 8-11.

This assistance is crucial, but in order for it to bear fruit fully, it must be integrated more effectively into the product development chain, in particular by strengthening Canada's process of technology transfer.

2.11.8 Lack of Growth Funding

The lack of capital has been mentioned repeatedly as a primary cause of why Canadian biopharmaceutical companies have been less efficient in commercializing innovations. At the same time, Canadian universities have taken to heart the goal of innovation and have started proportionally more companies (per GDP) than any other country. Our analysis indicates that Canadian venture capitalists (a primary source of capital for start-ups) perform as well as those in the US. This is consistent with data reported by the OECD in 2004 at a Science and Innovation Policy ministerial meeting, which ranked OECD countries on a number of innovative measures.[98] They concluded that:

- for VC investment , Canada ranked third;
- for share of high-tech sectors in VC funding, Canada ranked first;
- for amount of biotechnology VC funding (vs GDP), Canada ranked first.

Opinions expressed from participants in TRM surveys and focus meetings, especially from venture capitalists, were also consistent with this conclusion. Some maintained that there is not a shortage of venture capital at the early stage. Rather, they contended that the weakness in commercialization is due to premature start-up of spin-offs at universities before they are ready. Some felt that they were also funding too many opportunities because it allows risk to be pooled and increases the odds for success, given the common belief that only 20% of the firms they invest in will survive. They also complained that their start-up funds and development time were used for establishing proof-of-principle, strengthening IP and market assessment, activities that should have occurred at the seed and pre-seed levels, rather than for product development. Consequently, there was support for early-stage government funding of development and proof-of-principle, which can help add value to IP prior to attempts to commercialize. Because of the current situation, Canadian companies' IP strength is less than their US competitors', which results in more difficulty in supporting later-stage companies.

A similar conclusion was reached by BioQuebec in a study conducted by SECOR Consulting[99] to test the hypothesis that Quebec companies emerging from university research are created prematurely, thereby giving rise to many technologically weak ventures. The findings of the survey confirm this hypothesis, and partially explain the difficulties many biotechnology companies encounter in finding investors for technology that is often in the very early stages of development compared to American companies. The study reported that in nearly 80% of cases, Canadian technology transfer of university research occurs during the discovery phase or when validating the therapeutic target, while this happens in less than 20% of the US cases (Table 28).

The American experience demonstrates that transfers of technology developed in a university, either by granting a licence or by creating spin-offs, occur at a later date; that is, during the preclinical and medicinal chemistry phase. The SECOR study concludes that the absence of financing for applied

[98] Science and Technology Statistical Compendium, Science and Innovation Policy: Key Challenges and Opportunities, Meeting of OECD Committee for Scientific and Technological Policy at the Ministerial Level, (January 2004).
[99] SECOR Consulting, From Research to Marketing: Conditions for the Maturation of University Research in the Life Sciences, report to BioQuebec (February 2005).

research has driven universities to encourage creation of companies to finance technology development with private funding from venture capital. Venture capital has thus been diverted to finance research instead of being used to finance product development.

Table 28: Distribution of Spin-offs, 1998-2003, by Stage of Development at Spin-off

Regions Analyzed	Stage of Development	
	Discovery and target validation (%)	Medicinal chemistry pre-clinical testing (%)
Quebec	60	40
Philadelphia	10	90
San Diego	20	90
Raleigh	10	90

Source: SECOR Consulting, From Research to Marketing: Conditions for the Maturation of University Research in the Life Sciences, report to BioQuebec, February 2005.

These capitalization problems were also addressed by the Prime Minister's Advisory Council on Science and Technology (ACST) report on seed/pre-seed financing and commercialization skills.[100] It points out that while large tranches of government funding have been directed towards scientific research at universities and other centres, as well as to profitable companies that can make use of tax credits, there has been little or no reconsideration of funding at the seed and start-up level. Despite the success of programs such as IRAP, the CIHR Proof of Principle Program, and the NRC Industrial Partnership Facilities Program, only a small portion of government investment has been made available for the seed stage. The Council proposes that Canada consider three categories of funding:

- government public funding for non-profit research and for profitable companies;
- private market (VC) funding for early business start-up and development;
- a third category consisting of a joint public–private funding program for new business formation in the commercialization of scientific research.

Such third-category programs exist in other countries, including the Small Business Investment Companies (SBIC) in the US, the Yozma funds and Heznek Program in Israel, Australia's Seed Fund, New Zealand's Investment Funds, Finland's Industry Investment Initiative, Denmark's Vaekstfonde and Singapore's Technopreneurship Investment Fund.

2.12 Canada's Biopharmaceutical Commercialization Challenge: Conclusions and Recommendations

Previous chapters have highlighted the important technologies involved in biopharmaceutical innovation for the future. Canada has significantly increased investment in the discovery research technologies needed to maintain and grow a globally competitive position. Canadian researchers have maintained outstanding research productivity, as measured by the number of scientific articles published. It is imperative that Canada continue to make these discovery research investments; they form the foundation of innovative value creation.

[100] Roundtable on Seed/Pre-Seed Stage Venture Capital Financing and on Commercialization Skills, ACST Secretariat (March 2004).

While Canada has achieved a leadership position in research, the same cannot be said for the nation's ability to capture the downstream value that its research represents. Canadian entrepreneurs have outperformed other countries in the number of enterprises created. When biopharmaceutical enterprise creation is rated in proportion to economic output, Canada's performance has been outstanding.[101] But starting a lot of companies is far from being a strong basis for creating value.

Canada now has an historic window of opportunity to repair this weakness and build for itself a strong, globally competitive position in biopharmaceuticals. This opportunity arises because these new technologies are changing the way new products are discovered and developed, the way health care will be delivered, and the traditional integrated pharmaceutical company model. However, it is important to act swiftly, for that window may be closing rapidly. Unless Canada takes energetic remedial action, much of the most recent round of discoveries now contained in promising start-ups may be lost, and future Canadian discoveries may become dependent on non-Canadian firms for commercialization.

If this situation continues, some Canadian biopharmaceutical technology may well survive, but the value from commercializing Canadian research will be captured disproportionately by companies headquartered outside Canada — as long as the current approach to industry development continues. Up to now, Canada has ignored a fundamental weakness in its national innovation system — a major flaw in the progression from the research bench to commercialization.

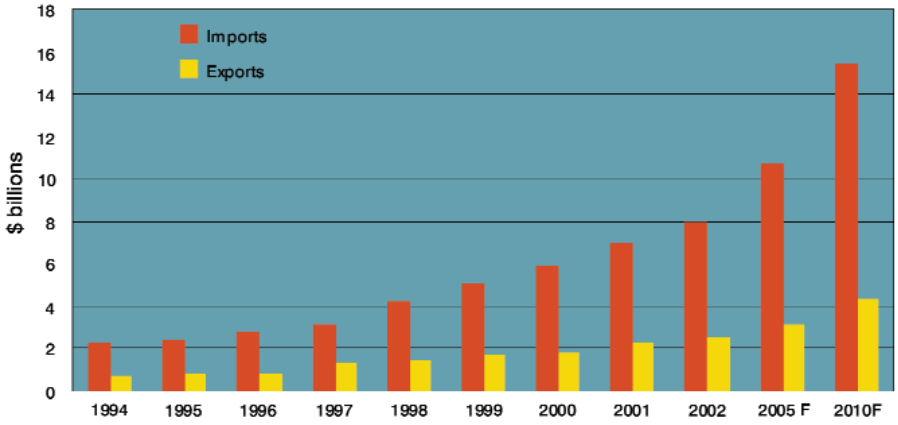
Canadian companies are too small to attract the kind of financing required to compete in North America. Table 25 cited above, which compares average and initial capitalizations in Canada and the US, illustrates the scale of Canadian disadvantage.[102] Remember, too, when considering this table, that a Boston-based start-up and a Montreal-based start-up are both competing in a North American environment. Why are Canadian valuations so much lower?

The implications of this weakness are far-reaching. Large investments in discovery research can be lost if Canadian companies are not able to move to commercialization in a timely way and therefore collapse or are acquired. Since acquisition typically results in the development of the commercial potential in a foreign country, under both circumstances the development and the value of increased jobs and capitalization are lost. Ultimately, this will affect Canada's ability to compete in a global, knowledge-based economy.

One indication of competitive weakness in this area is Canada's growing negative trade balance in pharmaceutical and medicinal products. Although our exports have grown, the growth of imports has been much greater (Figure 19).

[101] Ernst & Young, Beyond Borders (2003), p. 5.
[102] A Schincariol, President and CEO, Viventia Biotech, Barriers to Success: Access to Financial and Human Resources, CEO Roundtable (11 April, 2003), Toronto, slide 17.

Figure 19: Canadian Imports and Exports of Pharmaceutical and Medical Products



Note: Drugs & Medicines (SIC code 3741) comprises 45 categories of drugs for humans and animals.
Source: Ottawa Life Sciences Council Master Submission, On the importance of building Canadian biopharma manufacturing capacity, Executive Summary (2004).

As the figure shows, this deficit is expected to grow to $11.4B by 2010, compared with a $4.7B deficit in 2001 and a $1.8B deficit in 1997. Concomitantly, Canada's share of both domestic and global pharmaceutical production continues to decline. Canada is unlikely to develop a comparative advantage across the board in pharmaceutical products. But at the same time, the value of pharmaceutical exports must increase at the same rate or better than that of imports in order to maintain or improve the terms of trade in pharmaceutical products. Moreover, from the perspective of scientific achievements, Canada should not be ceding this competitive ground. Canada can do better.

2.12.1 Barriers to Successful Commercialization

The input received during the roadmap process and the analyses summarized here have identified the key barriers that limit the commercialization success rate of Canadian companies. They are:

- insufficient experienced senior management with the skills in product development and commercialization needed to guide the development plans and obtain funding;
- a lack of the timely and sustained capital required at the early seed phase to strengthen IP and complete proof-of-principle; and
- the consequent premature spin-off of start-up companies by universities, establishing companies with weaker patent and product portfolios.

These barriers are interrelated. Although Canada launches many new companies, these companies are started in weaker positions compared with US companies, having less capital to undertake development and protect IP. Moreover, because there is relatively low turnover of successful, experienced management in large pharmaceutical companies, there are few experienced product managers available to take charge in early stage biotech companies and make the commercialization-oriented business and product-development decisions that would improve results. There is also a cultural gap, in that most start-ups are managed by the researchers who developed the research, but lack commercialization experience. This list of weaknesses corresponds to the key criteria that investors use to make investment decisions. Private sector investors cite the following measures used in evaluation of a potential investment:

- an experienced, successful, management team capable of effecting product development and communicating with the business community;
- strong science and technology, but more importantly a sound IP position, preferably related to an enabling technology. Good proof-of-principle or very strong pre-clinical data is a key factor; and
- an attractive market opportunity, meaning the company has a business model that plots a trajectory to commercialization with attractive financial returns for investors and shareholders.

All these factors combine to present a 10-point picture of the problem facing Canadian commercialization:

- Canada relies on universities to undertake discovery research and new company start-up much more than any other country;
- Canada has a strong research/discovery capacity that generates many opportunities. Canadian researchers are as effective as those in other countries in output of new scientific discoveries, measured in scientific citations and invention disclosures. However, fewer of these discoveries lead to patents in Canada than elsewhere;
- Canada's level of commercialization is weak, ranking near the bottom among OECD countries;
- Canadian technology originating at universities and research institutes is launched in start-up companies earlier than the US;
- Additionally, there is a gap in the seed capital available to strengthen IP, complete proof-of-principle and review marketing potential. Canadian start-ups are funded at lower levels. An average US NIH grant is about $1M, compared with average initial funding of about $100K in Canada;
- The impact is that Canadian companies have fewer resources to complete needed early development and do not build as strong an IP portfolio;
- Government funding, used primarily to build infrastructure of research/discovery, is among the highest of OECD countries as a percentage of the government budget. The early private investors have to fund the development of the intellectual portfolio and pay for proof-of-principle research;
- Due to low capitalization and weaker patent positions, Canadian companies are competitively disadvantaged when they need to seek additional risk capital;
- Venture capitalists in Canada, the primary source of funds for early-stage and start-up companies, fund Canadian companies as well as those in the US;
- Business is the primary source of funds for commercial development, but provides only 75% of the level of support available to firms in the OECD countries. Canadian companies attain fewer strategic alliances, which is the primary source of capital for US biopharmaceutical companies. This is probably related to their weaker patent and patent portfolios.

Given that a root of Canada's commercialization problem is the premature birth of promising companies, then contributors to this problem can be identified at virtually every level of Canada's innovation system:

- Universities contribute by emphasizing the numbers of start-ups rather than the quality and strength of start-ups they produce;
- Government grant programs also contribute by awarding grants that emphasize scientific measures instead of business success measures. Some private investors maintain that there is

sufficient capital in Canada for strong companies, but that there are too many start-ups with insufficient strength;

- The mid-stage companies (attempting to complete proof-of-principle to Phase II) also receive lower investments, resulting in insufficient resources to complete clinical testing. Consequently, they resort to limiting product development to one or two products; a risky strategy that is often unsuccessful.

One consequence of the weakness of early- and mid-stage Canadian companies is that some Canadian investors look to the US and foreign locales to invest, since they can find companies with stronger patent positions and lower risk.[103] For both early- and mid-stage companies, the lack of experienced senior management with skills in developing products, designing the commercial business model and communicating it to investors, is also a limiting factor in Canada. An additional limitation on company growth is that Canada also lacks strong clusters of expertise and experience where people with all the skills assemble, creating an environment that encourages synergy and rapid progress.

The time is opportune for Canada to address these weaknesses as more and more technological advances are achieved. In fact, action must be taken quickly in order to protect the substantial research investments that are being made. One encouraging sign is that, as mentioned earlier, the genomics revolution is opening up economic advantages for Canada's research-intensive small and medium-sized companies.

Consider that the major impact of the new technologies is that researchers are now able to identify and screen large numbers of lead products that are more finely targeted to specific disease states. A consequence of this is that it will be possible to develop therapeutic products that are more effective, but only for the segment of the patients who can benefit. This contrasts with today's strategy of a more general-acting product that is used to treat large patient segments. As a result, although more products are available, the market potential for each product will likely be smaller, in the $200M range. There will probably be fewer blockbuster drugs in the billion-dollar sales range, which large pharmaceutical companies must produce in order to continue to grow and obtain the returns that justify the risk.

These new technologies present new opportunities for Canada to develop this industry since they are driving profound changes in the drug discovery process, the method of delivery of health care and the value chain of the biopharmaceutical industry.

This is an opportunity, since the structure of the industry will change, permitting the growth of companies with lower revenue drugs. The change is opportune for Canada, because the weakness of not having a large pharmaceutical industry infrastructure — often cited as a causal factor in the premature spin-off of early-stage companies — may not be as important in the future, while its integrated health care system is an advantage.

2.12.2 Eradicating the Barriers

Here's what has to be done: progress requires that all stakeholders, government, industry, academia and investors take coordinated action to implement solutions targeted to the barriers to success, rather than generate multiple dispersed programs. The main goal: to establish more sustainable companies.

[103] Harrison, op. cit., slide 11.

2.12.3 Winning Principles

The solutions should be based upon the following principles:

- Rely upon the private sector to use its expertise to make the primary assessment and pick winners;
- Utilize government programs to facilitate conditions and match funds;
- Ensure that academia, government and industry all participate;
- Do not place a limit on the number of start-ups, but establish criteria for funding that are directed to the barriers;
- Choose solutions that support all high technology sectors;
- Tweak existing government programs to include a focus on barriers;
- Focus action on the commercialization barriers.

2.12.4 Action Program

For an innovation strategy to deliver on Canada's scientific excellence, it must consider commercialization as an integral part of the innovation challenge. In order to do this, Canada should re-examine its existing programs of support for R&D and early-stage commercialization with the aim of generating more robust companies, which are able to attract investor capital. That means:

Encourage research spin-off companies to build up the management teams, their intellectual property positions and proofs-of-principle before advancing to private markets.

An examination of funding available for early-stage companies transitioning from research settings to commercialization suggests that programs now in place need to be made more flexible and to have more resources to accomplish this.[104] Some jurisdictions — notably the US — have created special programs (such as SBIR) pre-seed to accomplish this goal. Canada might achieve similar results through such existing programs as IRAP, TPC or the CIHR Proof of Principle program if the objective of enterprise-readying were to be made explicit and applications criteria appropriately adjusted to reflect commercial or business criteria.

Encourage university industry liaison offices to devote resources to readying companies for approaching capital markets.

In many cases, current emphasis is on rapid revenue generation from often-premature technology licensing. More appropriate would be to encourage universities or third-party technology evaluation funds to act as investment banks, combining where necessary different small companies and their technology to make a more attractive and robust new enterprise.

Initiate changes in both the immigration and taxation systems so that Canada can succeed in attracting supremely capable international managers to pilot Canadian companies.

There have been some positive changes in the immigration rules. In addition, some provincial initiatives — in particular those of Quebec — show the kind of imagination and initiative required. But to be fully effective, such programs need to be generalized to the national level.

[104] One example is the Small Business Industrial Research (SBIR) program designed to enable early-stage companies in strategic sectors to advance to proof-of-principle stages in order to maximize chances of successful commercialization.

Since these recommendations cut across government, academia and industry, it is further recommended that government facilitate the change by focusing national attention on the issue and solutions. Implementation of change can be assisted by having some central entity to direct the programs.

A more detailed set of follow-up actions to the above recommendations appears as an Appendix to this report.

Appendices

Appendix 1: Eradicating Development Barriers to Canadian Biopharmaceuticals

The numbers in brackets refer to the detailed descriptions of the proposed solutions at the end of the Table.

Barrier 1
Canadian companies start up too early with insufficient capital and IP protection.

Government Solutions	University Solutions	Industry Solutions
1. Redirect and increase existing grant programs and subsidies to early-stage technologies that demonstrate strong scientific principles, the potential to develop significant IP position and a business model that enhances the probability of commercial viability. 2. Modify IRAP, in light of other successful programs like the US SBIR, to: a. have additional funds for commercialization; b. ensure that the difficulty in obtaining funds is in line with the amount requested; c. cover business expenses such as preparation of a business plan, market research, business consultants. (1) 3. Implement a legal and fiscal framework for market innovation during the university phase of research. 4. Establish a single inter-government window. (2)	1. Have UILOs assess the patent strength and commercial relevance of the opportunity, not just focus on number of start-ups. 2. Improve IP and licensing procedures by recruiting more experienced patent and industry personnel. (3) 3. Establish a pre-incubation infrastructure in universities and university hospitals. (4) 4. Make available and/or easier to access research funding programs involving corporate–industry partnership. 5. Set up a proof-of-principle fund. (5) 6. Create joint public–private research consortia.	1. Organize industry associations to establish joint industry–university technology transfer office coordination to establish criteria and key success factors. This would assist in the early evaluation of new technologies and convey industry imperatives to universities. 2. Encourage the BDC to expand its competencies in biotechnology and assist in this early commercialization evaluation. (6)

Barrier 2
Mid-stage companies lack sufficient and timely capital resources to complete proof-of-principle on multiple products.

Government Solutions	University Solutions	Industry Solutions
1. Review and revise government programs to establish a more favourable fiscal and legal environment for investors in biotechnology. Examples: a. Encourage private, domestic and foreign investment in mid stage by providing incentives to adjust for the additional risk of investing in Canadian companies that require longer to establish patent protection and proof. Establish an investment fund of $200 million that will match private investment on a non-	1. Universities should harmonize the technology transfer process to become more aware of industry needs and constraints regarding patent strength and financing. (3) (10) (13)	1. Initiate promotional activities towards targeted institutions. a. Propose new financing vehicles and maximize existing capitalization instruments. b. Create a permanent showcase to encourage networking between companies and investors. c. Encourage associations to organize forums for communication between industry and government.

dilutive basis, perhaps to a limit of $10-15M, but for a minimum of three years.
b. Modify escrow rules following IPOs.
c. Provide fiscal incentives to individuals that invest directly into a biotech VC fund or a private biotech company such as the Régime action croissance PME in Québec.
d. Modify regulations to allow pension funds and insurance companies a portion of their assets in biotech VC funds.
e. Provide a government guarantee to protect insurance companies and pension funds against part of their potential losses for their investment in a biotech VC fund. (7)

2. Promote the biotech industry to financial angel network and fund managers.

3. Increase VC competency by hiring experienced pharmaceutical specialists to educate institutional investors on biotechnology investment opportunities. (8)

4. Create a super biotechnology investment fund or maximize existing funds by applying similar measures as above. (9)

Barrier 3
Lack of the experienced management at early and mid stage needed to commercialize.

Government Solutions

1. Continue support for currently sponsored biotechnology training programs, including training for managers. (10)

2. Consider support for a limited number of regional clusters to encourage and fund the assembly of experienced managers to act as business advisors to multiple early- and mid-stage companies.

3. Increase funding of business incubators to ensure more experienced personnel are recruited and fees can be paid for business consultants. (11)

4. Revise federal provisions where possible to enhance the ability of industry to recruit experienced managers from other countries. Examples:
a. Review immigration laws to facilitate immigration of researchers and senior managers and their families.
b. Provide tax holidays for foreign researchers and senior managers. (12)

5. Align job creation programs with IP creation, making SRED programs more efficient. (12)

University Solutions

1. Establish shortened training programs that emphasize industry criteria. (11)

2. Harmonize university programs with industry needs. (8) (11)

3. Create an international inter-university management training institute for the industry. (8) (11)

Industry Solutions

1. Industry should encourage mentoring programs. Examples:
a. Create a university–industry mentoring program.
b. Make investors more aware of their role in supporting company management.
c. Create a mentoring and sponsorship program.

2. Improve Board of Directors by adding experienced industry reps and more international representation.

3. Expand opportunities for networking to expand experience. Examples:
a. Develop a list of key business experts available to companies for boards, advisory committees or business consulting.
b. Make case studies available and circulate them.
c. Encourage networking activities between biotech executives and Canadian pharmaceutical and clinical research corporations.

4. Market the Canadian biopharmaceutical companies to U S and international companies as a means to attract employees. (14)

5. Organize industry–government forums.

Description of Potential Solutions

Modifications to IRAP's Mandate (1)

IRAP has a pilot program in Québec that covers business expenses such as market studies, development of a marketing strategy, cost-benefit studies and IP protection. The program is limited to 10 companies for the 2004-2005 period; since April 2004 four companies have benefited from this program. IRAP will cover up to 50% of admissible expenses with a maximum of $25K. This program is currently being reviewed.

Another program involving a federal government agency is also available in Québec. Canada Economic Development could invest up to $25K in companies registered in the pre-incubation program of the Québec Biotechnology Innovation Centre (QBIC). This investment takes the form of a non-guaranteed loan, and the company needs to invest 25% of the needed funds. This program has allowed the QBIC to attract start-up companies from other business incubators because of the companies difficulty in financing expenses such as business plan preparation, IP protection, market studies, legal and accounting fees.

Single Window (2)

Different ministries and government agencies have different financial assistance programs that could be of great help to biopharmaceutical companies. Going through the documents and the different Web sites is a full-time job that becomes rapidly very frustrating for entrepreneurs that are pulled in numerous directions. Some kind of central office should be set up to direct entrepreneurs to the programs that respond to their different needs.

Universities and Qualified Personnel (3)

Most university technology transfer offices would benefit from adding personnel with industry experience and building stronger relationships with their patent agents. The industry personnel could become employees or (preferably) act on a consulting basis. This approach would give the people responsible for university transfer technology a much better understanding of industry needs and its modus operandi. Access to a network of people responsible for the business development activities of companies in the healthcare sector would also be helpful. Funds to allow university to hire this specialized personnel have been lacking, and government assistance may be needed to support transfer technology offices in this task.

Pre-incubation Infrastructure (4)

An attempt has been made in Québec to establish a pre-incubation infrastructure when the provincial government created Valorisation Recherche Québec (VRQ), which obtained 50M$ to set up four Sociétés de valorisation to work with the entire province's higher education institutions as well as to finance different projects submitted to these organizations. As of today, the success of these groups has been, according to many experts in transfer technology, below expectations for different reasons. Furthermore, funding to these Sociétés de valorisation by the provincial government will end on March 31, 2006. Even if the experiment was not fully successful, this strategy should continue with the necessary modifications. Amongst the possible reasons mentioned for this underperformance are the following:

- lack of deliverables;
- lack of business experience among management;
- use of a model similar to the one used by UILOs;
- unrealistic objective (self-financing in the company's sixth year of operation);
- lack of focus — all types of technologies funded.

Proof-of-Principle Fund (5)

There are already a few proof-of principle funds: le Centre québecois de valorisation des biotechnologies (CQVB), the four Sociétés de valorisation, the CIHR Proof of Principle program and IRAP. Generally, the amounts available are insufficient, while other programs are dedicated to private companies only (that is the case of IRAP and CQVB). A "Canadian Biotechnology Proof-of-Principle Fund" of $10M a year should be made available to universities and managed by one agency. IRAP could be a suitable candidate to manage this fund because it is already involved in this type of program.

Improvement of BDC Evaluation Capacities (6)

The BDC has the mandate to invest in different sectors of the economy, but its analysts do not generally have a thorough understanding of the biotechnology industry. Furthermore, some of the experts that they recommend to assist companies in which they have invested or are considering investing do not have experience in the health care sector and therefore cannot contribute to the company's growth. The BDC should broaden its network to include more biotechnology experts.

A potential solution is to adopt the same strategy that the Caisse de dépôt et placement du Québec has recently chosen: mandate a specialized venture capitalist to manage their investments in the biotechnology sector, as well as their investments in other innovative sectors. In other words, the BDC could set up a subsidiary specialized in the biotechnology sector or the government could invest a portion of its funds in a specialized fund manager in biotechnology.

Investment by Insurance Companies and Pension Funds (7)

These companies are generally risk averse because they must retain the funds to meet their future obligations. The Canadian government could guarantee a portion of their potential losses, 50% for example, by some kind of insurance fund.

Our stock market agencies impose escrow rules that prevent original investors from exiting a company in a timely enough fashion to allow them to invest in other opportunities. In Canada, venture capitalists can trade only a certain percentage of their stock per quarter, based on their original position in the company, over an 18-24 month period. In the US, a venture capitalist can trade all its stock one quarter (90 days) after the IPO.

Increase VC Personnel Competencies (8)

See comments on points 3, 6 and 13.

Biotechnology Superfund (9)

Over the last few years, a number of unsuccessful attempts have been made to create such a superfund (such as Biopharma Drug Development Accelerator or BioMundis, both of which were dedicated to biotechnology follow-on funding). Governments should consider fiscal incentives to encourage the creation of this type of fund. Provincial governments should also consider investing in a biotech

superfund without involvement in its management but with conditions to ensure that most of the money is invested in Canadian companies or any other economic conditions they might impose. Governments should not impose social and political conditions. They could also consider giving fiscal incentives to individuals that invest in this superfund similar to those given to investors in labour funds.

Sponsored Biotechnology Management Programs (10)

Many universities have started giving business management programs specifically for the health care sector. In the province of Québec, l'UQAM and l'Université Laval have MBA programs for health care managers. Other universities, such as l'Université de Sherbrooke have developed pharmacology programs that incorporate a few management courses adapted to the health care sector. Governments should financially support the universities offering these programs and the students registered in them. They should also find incentives for companies that would encourage them to send selected employees to these programs. Government should continue to support currently sponsored biotechnology training programs, such as the Biotechnology Human Resource Council.

Funding of Business Incubators (11)

The survival rate of start-up companies enrolled in a business incubation program is far superior to that of other companies. A portion of the operating costs of business incubators is subsidized by the provincial and federal governments. In recent years, governments' contribution has been steadily decreasing, causing business incubators to increase their rates (limiting the number of companies that could afford their services) or to reduce the number of services they offer. Governments should increase their financial support to business incubators to at least previous levels. On the other hand, the governments need to also consider the investment they will make in recommendations 1, 4 and 5.

Tax Holidays for Foreign Researchers and Managers (12)

A federal tax holiday program similar to the one used in Québec should be developed for foreign researchers and managers, as well as for Canadians abroad who want to return to Canada.

Training and Industry Needs (13)

The biotechnology industry is experiencing an acute shortage of qualified managers. University training programs should focus on industry needs — not only to supply trained executives but to supply them in a timely fashion. Universities should make efforts engage with industry to better identify its current and future requirements for both research and management personnel.

Attract Qualified Personnel from the US and Other Countries (14)

Using its Foreign Affairs and Trade representatives, and working with local business associations, such as Montreal International, the Canadian government should develop a series of activities in key selected cities throughout the world to attract qualified research experts as well as experienced executives.

Appendix 2: Consultations

The Biopharmaceutical Steering Committee would like to thank all those who participated, or attended on behalf of participants, in our organized events. We would also like to thank others who reviewed the numerous drafts, concluding with the final report. Together we were able to bring to fruition the Biopharmaceutical Technology Roadmap.

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