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DETERMINANTS OF VENTURE CAPITAL SUPPLY IN THE CANADIAN BIOTECHNOLOGY SECTOR: FINANCING ISSUES, PERFORMANCE AND EVALUATION

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DÉTERMINANTS DE L'OFFRE DE CAPITAL DE RISQUE DANS LE DOMAINE DE LA BIOTECHNOLOGIE : ENJEUX ET DIFFICULTÉS, PERFORMANCE ET MODÈLES D'ÉVALUATION

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SUMMARY

DETERMINANTS OF VENTURE CAPITAL SUPPLY IN THE CANADIAN BIOTECHNOLOGY SECTOR: FINANCING ISSUES, PERFORMANCE AND EVALUATION

This doctoral dissertation contributes to the existing literature an in-depth analysis of the major financing issues and difficulties of Canadian biotechnology firms, an estimation of the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian firms, and finally, an evaluation of the adequacy of capital supply and demand in the sub-therapeutic segment of the Canadian biotech sector.

Analysis of the financing issues and problems encountered by biotech companies is based on in-depth interviews with supply stakeholders operating in Canada (the Montreal, Toronto, and Vancouver areas) and in the U.S. (the Boston, New York, and San Francisco areas). Seventy in-depth interviews were conducted between February and October 2001. The methodology used is similar to that used in Bergeron, Kryzanowski, Gadoum, and Beaulieu, 2001-a (Bergeron et al. (2001-a) hereafter) and identifies the financing issues and difficulties by stage of product and company development for the bio-pharmaceutical, ag-biotech, and bioenvironmental segments of the biotechnology industry. Our study extends the Bergeron et al. (2001-a) study by examining the observations and perceptions of the other primary party to each financial transaction, namely the supplier of funds. We built an interview guide used to collect general supply stakeholders' information and a semi-structured questionnaire in which six main dimensions that are relevant to biotechnology financing, retained from the existing literature, were systematically explored. This is the first study to examine, on the ground, the financing process of a biotech firm and to analyse the issues and problems surrounding it.

Capital supply estimates are obtained using a probabilistic model that we consider the most appropriate to capture the supply generating process that results from the complex

interactions between the various relevant factors affecting supply. The estimation involves simulations using initial values of key relevant variables, retained from the existing literature and validated through the interviews, that are expected to affect the flows of funds to biotech companies along with hypotheses about their mean and volatility and on their future behaviour as explicitly modeled by two stochastic processes. The variables used in the model are macroeconomic variables, market and sector variables, firm-specific variables and the global availability of funds in past years. We contribute to the existing literature by identifying the main financing sources, direct and indirect, to the biotech sector and their proportions in the Canadian economy. We also innovate in using a probabilistic model to capture the stochastic nature of the fundamental factors affecting the supply of funds. We believe this can be extended to other areas in the high-tech sector.

In order to evaluate the adequacy of capital supply and demand, we first estimate the capital requirements for the Canadian therapeutics sub-segment which, according to interviewees, shares over 80% of the total capital allocated to biotech activities, and is the only segment with available data about development costs and attrition rates, and a more complete and updated state of the pipeline of molecules for Canadian firms. Initial estimates of aggregate capital requirements are presented in Bergeron, Kryzanowski, Beaulieu, and Zorgati, 2001-b (Bergeron et al. (2001-b) hereafter). We re-estimate total capital requirements using an improved estimation method, new and updated data about development costs and attrition rates, and a more complete and updated state of the pipeline of molecules for therapeutics biotechnology firms. In addition, unlike Bergeron et al. (2001-b), we provide initial estimates of the aggregate external capital requirements of our Canadian sample. Second, we estimate the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian firms, and finally we produce a matching of expected demand and supply of funding and evaluate the volume of external funding likely to come from the U.S. and other financial markets. To our knowledge, it is the first attempt to characterize the adequacy of supply and demand in

the biotech sector in Canada. Such an effort is likely to prevent from any wrong effect of a shortfall of supply of capital on reasonable terms and costs that could impede Canadian firms to fully exploit their future growth opportunities.

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DÉTERMINANTS DE L'OFFRE DE CAPITAL DE RISQUE DANS LE DOMAINE DE LA BIOTECHNOLOGIE : ENJEUX ET DIFFICULTÉS, PERFORMANCE ET MODÈLES D'ÉVALUATION

Cette thèse contribue à la littérature financière par une analyse des enjeux et difficultés de financement des entreprises canadiennes de biotechnologie, une estimation de la capacité des investisseurs canadiens à rencontrer la demande anticipée de capital des firmes canadiennes et enfin, une évaluation de l'adéquation de l'offre et de la demande de capital dans le sous-segment thérapeutique du secteur de la biotechnologie au Canada.

L'analyse des points de vue des investisseurs sur les enjeux et difficultés liés au financement des firmes canadiennes de biotechnologie repose sur des entrevues approfondies réalisées avec des intervenants oeuvrant au Canada (régions de Montréal, Toronto et Vancouver) et aux États-unis (régions de Boston, New York et San Francisco). Un total de 70 entrevues ont été effectuées entre février et octobre 2001. L'étude vise à dégager la configuration structurelle de la problématique soulevée et ne vise donc pas une validation statistique de la population des investisseurs (directs et indirects) dans le domaine de la biotechnologie. La démarche adoptée est inspirée de Bergeron, Kryzanowski, Gadoum et Beaulieu (2004-a) et consiste à analyser un nombre suffisant de cas jusqu'à saturation, au sens d'une méthode d'analyse de cas, c'est-à-dire suffisamment pour qu'aucune autre dimension significative n'émerge. À cette fin, un guide d'entrevue comprenant six dimensions majeures retenues de la littérature financière est utilisé. Ce guide sert à faciliter l'analyse détaillée du contenu des entrevues et permet la construction de profils types des enjeux et difficultés liés au financement des firmes du domaine. C'est la première fois qu'une étude examine, sur le terrain, le processus de financement des entreprises de biotechnologie et les enjeux qui lui sont associés

L'estimation de l'offre de capitaux a été réalisée à travers un modèle probabiliste qui permet de capturer le processus générateur de l'offre résultant d'interactions complexes entre différents facteurs déterminants de l'offre. L'estimation requiert l'utilisation de variables exogènes que nous avons retenues à partir de la littérature économique et financière et validées à travers les entrevues. Aussi, l'utilisation de modèles probabilistes nécessite un état initial représenté par des valeurs initiales des variables pertinentes affectant l'offre de capital ainsi que l'adoption d'hypothèses quant à leurs moyenne, volatilité et leur comportement futur tel que spécifié par deux processus stochastiques. Les variables exogènes du modèle sont macroéconomiques, de marché, spécifiques aux entreprises et au secteur, et enfin l'historique de l'offre de capital dans le domaine de la biotechnologie. Notre contribution à la littérature financière est réalisée à travers l'effort d'identification des principales sources de financement, direct et indirect, dans le secteur de la biotechnologie ainsi que leurs proportions respectives. Nous avons aussi innové en utilisant un modèle probabiliste pour modéliser le comportement stochastique des variables clés affectant l'offre de fonds. Nous croyons que cette méthodologie peut être appliqué dans d'autres secteurs de la haute de technologie.

Dans le but d'évaluer l'adéquation entre l'offre et la demande de capital, nous avons estimé en premier lieu les besoins en capitaux nécessaires pour compléter les composés en place dans l'ensemble des firmes canadiennes appartenant au sous-segment thérapeutique. Plus spécifiquement, les capitaux nécessaires sont estimés selon deux types d'analyses : une analyse statique et une analyse dynamique. L'analyse statique porte sur les capitaux requis pour compléter les molécules thérapeutiques en cours de développement, c'est-à-dire pour, en quelque sorte, compléter le développement du « pipeline » actuel de composés dans les firmes. L'analyse statique et l'analyse dynamique portent sur les capitaux nécessaires, en faisant abstraction des réserves financières présentes des firmes. Cette estimation repose sur des scénarios tenant compte, entre autres, des estimations disponibles relativement aux coûts de développement à chaque étape ou phase, des taux d'attrition (taux d'échec ou taux de

passage d'une phase de développement à l'autre) et des caractéristiques propres au sous-segment thérapeutique. En deuxième lieu, nous avons évalué la capacité des offreurs canadiens de capitaux à rencontrer les besoins des entreprises canadiennes pour enfin produire des scénarios d'adéquation entre l'offre et la demande de capital ainsi qu'une estimation du volume de financement étranger pouvant être en besoin pour combler un éventuel manque de financement. À notre connaissance, cette étude constitue la première tentative de caractérisation de l'adéquation de l'offre et de la demande de capital dans le secteur de la biotechnologie au Canada. Cet effort est d'autant plus valorisé puisqu'il constitue une base de réflexion et de prévention contre tout manque de financement susceptible d'entraver la croissance de ce secteur.

Mots clés : Capital de risque, investissement, financement de la biotechnologie, demande de capital, offre de capital.

CHAPTER 1

INTRODUCTION

A more in-depth knowledge of biotechnology financing-related issues and problems is important for many reasons. Small and medium-size enterprises represent a large proportion of the Canadian biotechnology firms in number. Many of them have already entered, or are in the process of entering, the pre-clinical and/or commercialization stages in which capital requirements are larger. Furthermore, the number of products in the product pipeline is growing rapidly. It is reasonable to assume that the aggregate capital requirements of Canadian biotechnology companies will increase significantly. Although financing is considered a key development dimension, there is relatively little information available on how much capital is required, and on the difficulties encountered by companies when seeking financing. Inadequate capitalization affects the competitiveness of Canadian biotechnology companies and makes them potential acquisition targets. Strengthening competitiveness is also a major issue given the significant economic advantages associated with production and commercialization. Therefore, a better understanding of the financing issues and concerns faced by Canadian biotechnology companies is a pre-requisite for evaluating whether Canadian financial markets can provide sufficient access to capital, and for implementing policies to encourage the development stages with the greatest profit potential to be undertaken in Canada.

Biotechnology industry players are unanimous that their research-focused industry must do a strategic about-face and focus on commercializing products. Therefore, facilitating access to capital is a priority. Many existing companies are entering or will soon enter the development and commercialization stages where financing is particularly critical. Paradoxically, little information is available on stage-related financing issues and difficulties. Specific questions that need to be answered include: What are the capital requirements? Can Canadian financial markets provide sufficient access to capital?

What types of financing problems are encountered in this respect? What are the significant concerns of typical supply-side stakeholders?

This study provides answers and tools for though on the issues mentioned above and extends the literature by characterizing the supply of capital for Canadian biotechnology firms and evaluating the adequacy of capital supply for funding Canadian companies by estimating the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian firms.

Our work has two main components. The first of these is a detailed analysis of the viewpoints of various suppliers of capital about the financing-related issues and difficulties facing Canadian biotechnology companies. Given the structure of the biotech sector in Canada with small and medium-size enterprises representing a large proportion of the Canadian biotechnology firms in number and that many of them are in the process of entering, the pre-clinical and/or commercialization stages in which capital requirements are larger, it is reasonable to assume that the aggregate capital requirements of Canadian biotechnology companies will increase significantly. Although financing is considered a key development dimension, there is relatively little information available on the difficulties encountered by companies when seeking financing. Inadequate capitalization affects the competitiveness of Canadian biotechnology companies and makes them potential acquisition targets. Our analysis allows us to address such questions as whether Canadian financial markets can provide adequate access to capital and provides us with descriptive evidence on the problems and concerns faced by suppliers of capital. To our knowledge, this is the first attempt to examine the financing process of a biotech firm and to analyse the issues and problems surrounding it.

The methodology used in this part of the study is based on the pioneering work of Bergeron et al. (2001-a)[1] and identifies the financing issues and difficulties by stage of commercialization and company development. The approach is similar to that used in analyzing cases (i.e., a sufficient number of cases is analyzed until no other significant dimension emerges). For this purpose, we use an interview discussion guide based on the commercialization and development stages in Jolly (1997). This facilitates interview analysis, and the construction of the profiles for the financing-related issues and difficulties encountered by a typical biotechnology firm. Following Bergeron et al. (2001-a), the purpose of this study is to determine the structural configuration of the financing issues discussed, rather than to attempt a statistical validation of the importance of these issues for the population of supply-side stakeholders.

The issues and challenges of biotechnology investing in Canadian markets are identified using in-depth semistructured interviews with a sample of 70 specialists from both American and Canadian capital supply stakeholders. These participants include:

- Venture capitalists involved in seed financing and the subsequent stages of development;
- Investment bankers involved in IPO and subsequent stock issues;
- Capital market specialists from the Montreal, Toronto and Canadian stock exchanges, NASDAQ, and the New York Exchange;
- Alliance specialists from large pharmaceutical firms;
- Bank and public entities that are involved in biotech financing; and
- Canadian government officers involved with grants, fiscal assistance and tax credits.

A total of 70 in-depth, semi-structured interviews were conducted in Canada and in the U.S. between February and October 2001. In accordance with the methodology, six of these interviews were performed prior to the study to validate and finalize the interview

[1] See also Bergeron, Kryzanowski, and Zorgati (2002)

guide. Of the 63 retained interviewees, 37 are supply stakeholders operating in Canada and 26 in the U.S. Each interview was taped, and a corresponding verbatim written record was prepared to assure the quality of the detailed analysis. The participants identified several issues and challenges, which were categorized according to the investment's technological opportunity, the firms' management expertise, and its financial potential.

The second main component of this study presents an evaluation of how adequately capital supply meets capital demand for the Canadian therapeutics sub-segment of the industry. This effort is made in two steps.

First, we estimate the capital requirements for the Canadian therapeutics sub-segment which, according to interviewees, shares over 80% of the total capital allocated to biotech activities, and is the only segment with available data about development costs and attrition rates, and a more complete and updated state of the pipeline of molecules for Canadian firms. The stream of estimated capital requirements for the biotechnology sector in Canada and what these estimates imply in terms of the development of this sector were initially presented in Bergeron et al. (2001-b). These estimates strongly indicate an unprecedented increase in capital requirements in the therapeutics sub-segment. They also clearly stress the importance of adequate planning on the part of users and providers of capital if the capital appetite of this segment is to be adequately satisfied in the foreseeable future. We re-estimate total capital requirements using an improved estimation method, new and updated data about development costs and attrition rates, and a more complete and updated state of the pipeline of molecules for therapeutics biotechnology firms. In addition, unlike Bergeron et al. (2001-b), we provide initial estimates of the aggregate external capital requirements of our Canadian sample.

The capital required is estimated using both static and dynamic analyses with no adjustment made for the financial reserves currently held by firms in the sample. The

static analysis generates estimates of the capital required to bring products currently in the product pipeline up to market entry. These estimates are based on estimated development costs at each stage, estimated attrition or failure rates (i.e., the rate of not passing from one development stage to the next), and on certain factors specific to the therapeutics sub-segment. Estimates of the products currently in the product pipeline are elicited from the 2001 pipeline portrait of 171 Canadian public and private companies (Industry Canada, April 2001). Despite the inherent limitations of this estimation approach (particularly for the basic or discovery phase), we are able to objectively quantify capital requirements for the scenarios used.

The dynamic analysis extends the static analysis. By assuming growth in the number of products entering the pipeline annually over the initial five years, we analyze the evolution of capital requirements for various growth rate assumptions. Estimates of capital requirements for the other two segments (ag-biotech and bioenvironmental) are not provided herein. First, only limited information is available on the state of the pipeline for the ag-biotech segment. Second, cost and attrition rates are not available for these two segments, or for any other biopharmaceutical sub-segment other than therapeutics (i.e., diagnostics, drug delivery, systems or companies providing specialized scientific services).

Second, we estimate the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian firms, and finally we produce a matching of expected demand and supply of funding and evaluate the volume of external funding likely to come from the U.S. and other financial markets. For this purpose, we use a probabilistic model that we consider the most appropriate to capture the supply generating process that results from the complex interactions between the various relevant factors affecting supply. The estimation involves simulations using initial values of key relevant variables, retained from the existing literature and validated through the interviews, that are expected to affect the flows of funds to biotech companies along with hypotheses about their mean

and volatility and on their future behaviour as explicitly modeled by two stochastic processes.

The variables used in the model are macroeconomic variables, market and sector variables, firm-specific variables and the global availability of funds in past years. We contribute to the existing literature by identifying the main financing sources, direct and indirect, to the biotech sector and their proportions in the Canadian economy. We also innovate in using a probabilistic model to capture the stochastic nature of the fundamental factors affecting the supply of funds. We believe this can be extended to other areas in the high-tech sector. To our knowledge, it is the first attempt to characterize the adequacy of supply and demand in the biotech sector in Canada. Such an effort is likely to prevent from any wrong effect of a shortfall of supply of capital on reasonable terms and costs that could impede Canadian firms to fully exploit their future growth opportunities.

In its most general goals, our study is related to the large private equity financing literature that studies the investment schemes and the potential agency problems related to them. Theoretical models such as Holmstrom (1982), Gompers, Blair and Hellman (1998), and Ireland (2003) examine the distortions in managerial behaviour that arise when the market is trying to learn the ability of a decision maker. Because direct observation of investment contracts in the technology industry, especially for start-up and early-stage ventures, is rare, there is only a small empirical literature on issues surrounding the investment process, the potential agency problems and the ways private equity investors address them. While this study may improve understanding of investment stakes in the biotech sector in Canada it is more generally considered as part of a large problematic for corporate insiders and outsiders dealing with different perceptions on investment terms and conditions.

The main goal of our research is to characterize the supply of capital for Canadian biotechnology firms. The study has two main objectives. The first objective is to

identify the issues and difficulties from the viewpoint of the suppliers of capital by using a methodology similar to the one used to characterize demand. The second objective is to evaluate the adequacy of capital supply for funding Canadian companies (therapeutics sub-segment) by estimating the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian firms, and to evaluate the volume of financing from the U.S. and other countries needed to satisfy any shortfall in the financing requirements of Canadian biotechnology companies.

The remainder of the study is organized as follows. The next section presents a comprehensive review of the literature on the financing of biotechnology firms, especially with regard to the relevant dimensions to the decision to finance a given project or firm. Section 2 presents a synthesis and analysis of financing-related issues and difficulties based on comments elicited from the interviewees. We discuss the important concerns, and what concerns should be analyzed in more depth in subsequent studies to better understand the financing-related issues and their relevance. The methodology used to collect the interview data and a description of the sample precedes this synthesis and analysis. Section 3 presents general methodology for estimating capital requirements and updated scenarios presenting estimates of the capital required to bring products currently in (or expected to enter into) the pipeline of products up to market entry for the sample of Canadian companies in the therapeutics sub-segment. Two sets of estimates of the capital potentially available to Canadian companies follow in Section 4. One set is based on evaluations from a probabilistic model and the other from an empirical documentary approach. In Section 5 various scenarios matching the demand and supply estimates complete this important step of the study. Finally, Section 6 presents our conclusions as well as suggested areas for further research.

CHAPTER 2

REVIEW OF THE LITERATURE

This literature review examines the financing-related issues and concerns of biotech firms as they are addressed in the existing financial literature. Dimensions that may be relevant for characterizing the supply of capital to Canadian biotech's from the viewpoint of capital supply siders are examined.

The financial literature dealing with biotech financing issues is very limited for two major reasons. First, the biotech domain is fairly new and has highly distinctive features that limit the relevance of the more traditional literature on firm financing. For example, the development stages of biotechnology firms are fairly long, capital intensive, and are subject to high failure rates. Second, the capital-intensive biopharmaceutical segment, which is the most important, is highly regulated compared to other technology sectors.

A more detailed and relevant literature exists for venture and technology firm financing. Technology firms in the early stages of their development exhibit general characteristics that are similar to biotech firms. These characteristics are a high proportion of intangible assets like R&D and patents, the highly strategic role of human resources in the firm's value creation process, and the high volatilities and expected returns that characterize many investments of hi-tech firms. Though the distinctive features of biotech firms constitute an important challenge, the financial literature facilitates our effort to identify the relevant issues in biotech financing.

During the last two decades, the biotechnology revolution has resulted in phenomenal advances in the understanding and treatment of many diseases (Oliver, 1999). The Canadian biotechnology industry is a key sector with an important number of small firms that are short of equity but are keen on selling in specialized markets around the

world. Biotech companies in the nascent stages of developing products, such as drug discovery firms, have not yet had the opportunity to sell these products in the market. Managers of these early stage companies are still faced with the challenge of attracting and retaining investors in the absence of sales revenues. Thus, as the Canadian biotechnology industry moves further into the uncharted territory of drug discovery, it must make convincing arguments to interest investors.

Biotechnology is a very capital-intensive business (Robbins-Roth, 2000). It follows that a major challenge for biotech firm is the timely and ongoing acquisition of adequate funding. This activity requires careful assessment of the firm's ongoing needs along with a clear understanding of the various options for accessing capital. The purpose of the present study is to characterize the supply of capital for Canadian biotechnology firms. Our objective is to identify the issues and difficulties encountered by suppliers of capital when dealing with Canadian biotech firms. Characterization of demand has already been completed by identifying the financing-related issues and difficulties from the viewpoint of Canadian Biotechnology company executives (Bergeron et al. 2001-a), and by estimating the capital requirements for the therapeutics sub-segment of the Canadian biotechnology industry (Bergeron et al. 2001-b).

The supply of funds for biotechnology firms is not well documented in the literature but some authors have documented the supply of venture capital. Gompers et al. (1998) suggest some critical variables to explain the supply of funds in venture capital. At the macroeconomic level, these variables include the state of the economy, interest rates, the expected rate of return in the biotech segment, financial institution regulations, which prohibit or restrict investment in the segment, and capital gains taxes.

The development of a start-up investment in biotechnology is likely to go through several phases (Hall, 1992; Gompers, 1995). In the beginning stages, the venture consists essentially of the founders. These people with ideas may have some assets (a

working system, or a patent) but often little or no money for equipment and expenses. Therefore, they need an initial injection of funds (seed investment) to help them get started and to both develop their ideas and build the business to the point at which it becomes more attractive to outside investors. Working capital is generally very scarce at the beginning of a company's life (a few hundred thousand dollars). The initial investment is indeed very risky since a large percentage of seed funding ends in failure (Prager, 1999; Clements, 1996; Dawson and Collons, 1986).

Within about one year, the seed investment will be exhausted but probably with no product or service yet ready for the market place. The firm will need more money. The team will have prepared a business plan that will map out the next stage of the company's development and prepare for first round venture capital funding (Fried, 1994). At this point, funding requirements may be several times greater than the original seed-funding amount (Feen, Liang, and Prowse, 1995; Ehrlich, De Noble, Moore, and Weaver, 1994; Wright, 1998).

By the second or third year, the product(s) or service(s) being developed may be nearer the market but a second round of funding is needed. In the fifth or sixth year, the company may become a public corporation by offering shares for sale to the public. The principal motivation for going public is to obtain capital on terms more favourable and in amounts that are greater than may be available through other channels. Substantial amounts can be raised in public equity markets to fund working capital, research, development, marketing and manufacturing activities, as well as facilities (Robbins-Roth, 2000).

The availability of venture capital to support biotechnology ventures is crucial to the continued vitality of Canadian biotechnology firms. Venture capital funds invest money in these enterprises because they provide an opportunity to partake in unusually high returns as compensation for the unusually high risks involved in biotechnology ventures

(especially start-up ventures) but their role is open to discussion (Neidorf and Writer, 1999).

The Canadian venture capital industry has considerable financial and management resources. According to the Canadian Venture Capital Association (CVCA), Canadian venture capitalists financed more than 800 firms and invested almost $4.9 billion by the end of year 2001. They have some $20.2 billion under management and about $6.2 billion available for investment. The industry disbursed about $1.1 billion in life science companies, with biotechnology receiving more than half ($842 million). As reported by the CVCA, there was an upward trend favouring early stage companies with investments in company start-ups and seed financings totalling over $2.9 billion. Given that a large number of biotechs in Canada are early stage companies, this tendency must be considered as being encouraging for the expansion of the sector.

The transformation of science into technology is mediated by business forces and brings together two sets of people whose outlooks, specialized knowledge, and professional languages are very different and often out of touch with each other. Many of those charged with making financing decisions regarding science and technology have little or no understanding of scientific process or the culture in which it operates. On the other hand, many people who do understand technological development are poorly informed about financial and business matters. A chasm of knowledge and interest divides these two communities and hinders the progress they both seek. Whether the demand for funds by Canadian biotechs has been and will be satisfied appropriately needs to be explored further.

Venture capital investments are made on the basis of the investor's assessment of the business prospects of the venture and the ability of its management team. Doucet (2000) suggests that managers of early stage companies must have a good story to tell potential

shareholders. The story must include good quality science and technology, a winning management, and fine intellectual property.

Scientific due diligence is required to assess the quality of the science and the technology. It is a crucial step for investors to make a decision about a biotech project. Also, products (drugs) under development should have clear advantages over those already available at the neighbourhood pharmacy. They must address a commercially viable market that is both sufficiently large and has the potential to grow.

Another critical requirement of investors is the presence of a strong management team, particularly if the original founders are scientists without business experience (Barney, Spencer, and Reve, 1994). Investors will be very keen to ensure that their investment is in the hands of somebody who knows how to run a business, especially a start-up.

Investors place an equally great emphasis on the intellectual property (IP) that the company may own. They make a careful review of the IP before investing (Narin, 1995; Lerner, 1994). Biotech companies must retain the rights to manufacture and market at least some of the products that emerge from their research laboratories in order to build stockholder value and justify a healthy market valuation for the company. Without strong patents and licenses governing the composition and use of the compounds under development, competitors who could make off with their "meal" can outmanoeuvre a biotech firm! Investors follow when the IP is "rock-solid", well-protected, covers a wide geographic base, and extends well into the future. This suggests that issues and difficulties that capital supply siders may encounter when considering or declining biotech projects need to be explored.

Another investment consideration is the perception by the potential investor of the risk/reward consequences of investment. Evaluation of risk and putting together a financial structure to deal with it are both important. Venture capital investment must

aim for high rates of return over a relatively short time period because the investors know that, in spite of their best efforts to spot a success, they will often be wrong. Because the risk of failure is so high, the return on the successful project must more than compensate for the losses or the whole business of investing in high-risk ventures if such investing is going to be worthwhile. There follows an important question. How is the increased value of the investment to be realized? In the parlance of the industry, "what will be the exit route? Thus, the perception that investors have about risk and return when dealing with Canadian biotech firms is a second dimension of the biotech investment decision that needs to be explored further.

As suggested by Chidley (2000), the biotech sector is unpredictable and risky. Whether to invest in biotech depends on whether the investor knows what he is doing, how patient he is, and whether he has a strong tolerance for volatility. The unpredictability of the biotech sector, the gestation time (time to get products or drugs to market) and the possibility of failure to reach the critical mass necessary for public funding, are factors of risk that may be disadvantageous and may affect the motivation of suppliers to fund and support Canadian biotech companies.

A third dimension of the biotech investment decision is the difficulty in valuing biotech firms. Large, established companies with earnings track records in stable business sectors are easier for investors to assess than growth companies. Biotechnology companies are, in a sense, all "potential" and have little or no track record. Therefore, it is more difficult for investors to assess their prospects (Hull, 1999; Trigeorgis, 1996). Real options models offer potential avenues to value biotechnology projects (Kellog and Charnes, 2000; Amram, and Kulatilaka, 1998), but they are often seen as complex and difficult methods to implement by practitioners. One way to understand how values are determined in this "marketplace" is to ask practitioners about their valuation methods, and to what extent the difficulties to value biotech projects may be the cause of funding in stages as mentioned by the biotech company executives in Bergeron et al. (2001-a).

Boer (1999) suggests that a simple approximation of value is possible by simply examining the R&D funds the company has spent and the amount contributed by founders (Chan, Lakonishok, and Sougiannis, 1999). Thus, the level of owner commitment and financial participation in the project is a fourth dimension of the biotech investment decision that needs to be further examined.

Asking for funding also requires a biotech company to disclose information relating to its science, technology, business and financial conditions. These requirements may force a company to suffer the competitive disadvantage that results from disclosure of sensitive information such as the identity of products in research (molecules and drugs) and the methods and costs of research. Company executives interviewed in the first phase of this study mentioned that the disclosure of information could be an impediment to funding. Biotech founders may be hesitant or wary of disclosing information because of their fear of losing exclusivity or failing to retain control over their project. This is a fifth dimension of the biotech investment decision that needs to be explored further.

Until recently, the financial health of a biotech firm was largely measured in terms of the interest and funding from venture capitalists and public markets. Oliver (1999) and Robbins-Roth (2000) note that big pharma assets, loans, and even intellectual property have forced a re-evaluation of the market value of biotech firms. Alliances between small biotech start-ups and big pharmas are now an important form of industry financing. Small biotechs need such alliances with big pharma companies for survival. The big pharmas need different alliances with the biotechs to hedge their bets and to ensure a steady flow of innovations. Usually, a small R&D firm partners with an international pharmaceutical company. Big pharmas have deep pockets and considerable experience in R&D, marketing, manufacturing, regulatory know-how and other resources. Furthermore, Champsi (1998) suggests that for companies that win the support of investors, the opportunity for mergers and acquisitions could be used as a

catalyst to raise additional capital more easily. Champsi notes that investors are concentrating their holdings in companies with "critical mass", requiring them to pursue mergers and acquisitions as a requisite to future financing and liquidity. Thus, the sixth dimension of the biotech investment decision that needs to be explored is strategic alliances/mergers and acquisitions.

Government commitments and/or guarantees are used to manage risk (Lerner, 1999; Fox, 1996; Eisenger, 1993; Irwin and Klenow, 1994). Federal and provincial governments in Canada have industrial policies and regulatory frameworks that may support or even favour the biotech sector. Thus, the final dimension of the biotech investment decision that needs to be explored is the perceptions of government policies and tax structure in Canada.

CHAPTER 3

FINANCING-RELATED ISSUES AND DIFFICULTIES FROM THE POINT OF VIEW OF SUPPY SIDE STAKEHOLDERS

3.1 METHODOLOGY

The methodology used to satisfy the first objective consists of creating profiles of the issues and difficulties perceived by the main stakeholders. These issues and difficulties are identified and described through the use of semi-structured interviews and an analysis chart revised interactively with suppliers of capital. In this respect, the methodology is similar to the one used previously to establish the viewpoint of users of capital.[2]

The approach involves a characterization of the viewpoints of capital supply stakeholders. To identify, document, and analyze financing-related issues and difficulties, we begin with a thorough analysis of the detailed verbal record from each interview. This facilitates the selection of the issues retained for subsequent analysis. The detailed analysis of the perceptions of the interviewed supply stakeholders provides the raw data upon which we evaluate the measures that could be implemented to improve access to capital.

The completion of case studies helps to determine qualitatively the structural configuration of the financial issues discussed. This approach involves analyzing additional cases until saturation (i.e., until no other new significant dimension emerges). In order to ensure a sufficiently detailed analysis, we select a relatively large number of supply stakeholders to interview.

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[2] See Bergeron, M.Y., Kryzanowski, L., Beaulieu, P. and Gadoum, Y., 2001-a, Financing-related issues and difficulties for Canadian biotechnology companies, International Journal of Biotechnology, Vol. 3, Issue 3.

3.1.1 COMPANY COMMERCIALIZATION PROCESS AND DEVELOPMENT STAGES

We use Jolly's (1997) classification of the commercialization process (see Appendix C). This classification of the value creation process includes five sub-processes that are similar to the conventional stages of technological innovation. These five sub-processes are: 1) imagining, 2) incubating, 3) demonstrating, 4) promoting, and 5) sustaining.

Jolly (1997) argues that these five sub-processes of technological innovation correspond quite well to the main categories of sources of funds and financing methods used by technology-based firms. Therefore, it is relevant to use this approach as a backdrop for analyzing the evolution of financial requirements in the various sectors of the biotechnology sector, and for building a typical profile by sub-process and/or stage of commercialization.

Our case analysis procedure consists of the following stages:

1) Conduct an in-depth literature review of biotechnology financing issues.
2) Design a semi-structured discussion guide of financing-related issues that is superimposed over each of the sub-processes of Jolly's model, and is pre-validated with several target firms.
3) Select a representative sample of supply-side stakeholders in each of the three previously mentioned segments.
4) Conduct the field interviews.
5) Conduct an in-depth analysis of the interview content.
6) Construct the typical profiles.

3.1.2 RELEVANT DIMENSIONS OF THE ANALYSIS AND DISCUSSION GUIDE USED

The six main dimensions, which were retained following the literature review, are systematically explored in the interviews. Interviewees were also free to suggest other relevant dimensions. The main dimensions used include:

- Types of projects
- Differences in perceptions of risk and return
- Degree of founder commitment and financial participation in the project pipeline
- Disclosure of information
- Relevance and use of strategic alliances as a source of financing
- Government commitments and/or guarantees for managing risk
- Other dimensions

The interview guide used to collect general supply stakeholders' information and the semi-structured questionnaire are presented in Appendix C.

3.2 DESCRIPTION OF THE INTERVIEW SAMPLE OF SUPPLY STAKEHOLDERS

Seventy in-depth, semi-structured interviews were conducted in Canada and in the U.S. between February and October 2001. In accordance with the methodology, six of these interviews were performed prior to the study to validate and finalize the interview guide. Since these interviews were not considered for analysis purposes, the interviewees are not included in the list presented in Appendix D. The interview guide presented in Appendix C is used to identify the financing-related issues and difficulties of Canadian biotech companies from the viewpoint of the capital suppliers. Other information gathered in the course of the interviews is also combined with secondary data sources to evaluate the capital raised by the biotech sector during the last two years, and to estimate the amount likely to be invested during 2001 and 2002.

Of the sixty-three retained interviews, 37 involved supply stakeholders operating in Canada and 26 in the U.S. They involved a representative sample of supply siders: venture capitalists, institutional investors, investment bankers, banks and Para public entities involved in biotech financing, and other stakeholders including capital markets and biotech analysts, alliances and M&A specialists, and public officers. Each interview was taped, and a corresponding verbatim written record was prepared to assure the quality of the detailed analysis. The average length of an interview was 50 to 60 minutes.

Interviews conducted in Canada involved stakeholders from Montreal, Toronto and Vancouver. U.S. interviews involved a representative sample of capital suppliers from the main U.S. biotech clusters, namely, San Francisco, Boston and New York. As shown in Figures 3.1 and 3.2 below, the Canadian sample contains nineteen venture capitalists, five investment bankers, five institutional investors and eight others. The U.S. sample includes fourteen venture capitalists, eight investment bankers and four others.

Figure 3.1: Breakdown of the Canadian sample by type of stakeholder

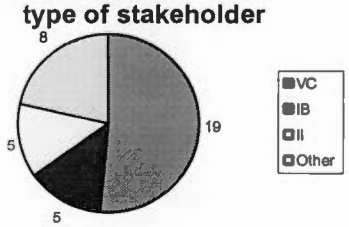
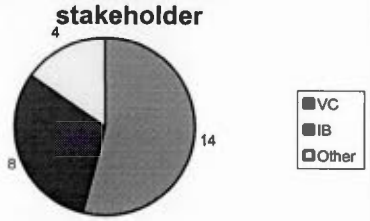


Figure 3.2: Breakdown of the U.S. sample by type of stakeholder



Canadian venture capitalists interviewed during the study have about $6.5 billion under management, as of December 31, 2000. Over 40% of this amount or $2.6 billion is invested in biotechnology, mostly within Canadian firms. This amount in biotechnology is expected to increase by about $800 million over the next two years. Five Canadian

interviewees were institutional investors with capital under management of over $4.5 billion, and 18% of this amount is allocated to biotech investments in Canada. These interviewees alone intend to invest an additional $400 million in the Canadian sector over the next two years.

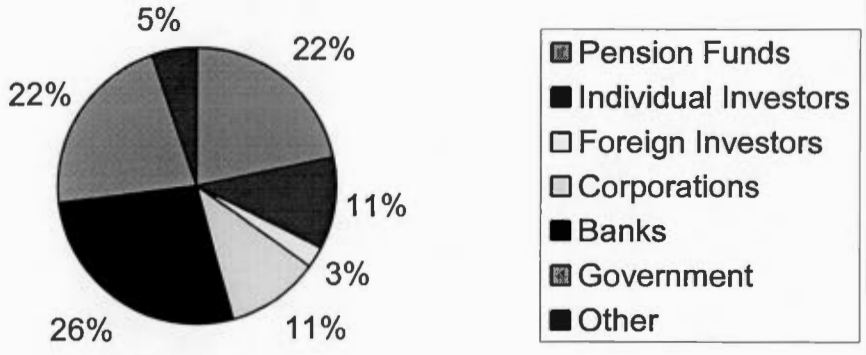
The U.S. sample mainly consists of venture capitalists and investment bankers. Interviewed U.S. venture capitalists have $9.5 billion under management, of which 63% is invested in biotechnology. Only 2% of the $9.5 billion is invested in Canadian firms. Table 3.1 summarizes the quantitative information gathered from Canadian and U.S. interviewees.

Table 3.1. Quantitative information gathered from the Canadian and U.S. interviewees

	Number	Capital under management (millions)	Percentage invested in biotech (average)	Percentage invested in Canada	Intention to invest over the next one to two years (additional, millions)	Desired rate of return (average)
Canada						
VC	19	6,494	40	92	800	25%
Inst. Inv.	5	4,650	18	100	400	20%
U.S.						
VC	14	9.443	63	2	978	50%

As shown in figure 3.3, banks, pension funds and governments are the most important potential sources of capital for investment in the biotech sector. Corporations and individual investors are second (with a proportional share of 22%), and retail and foreign investors, foundations and other sources account for the remaining 8% of the total capital potentially available for investment.

Figure 3.3: Sources of funds of Canadian suppliers interviewed



3.3 SYNTHESIS AND ANALYSES OF FINANCING-RELATED ISSUES AND DIFFICULTIES

This section identifies the main financing-related issues and difficulties addressed by the interviewees. The profiles contain representative summaries of the perceptions of the interviewees as identified by the detailed content analyses of the interviews in order to provide a concise description and a preliminary analysis of financing-related issues and difficulties. This preliminary analysis considers information for every relevant dimension identified in the review of literature presented in section 2.

3.3.1 TYPE OF PROJECT TO FINANCE

The type of project is an important determinant in the relative difficulty encountered in obtaining financing. The fund requester needs to demonstrate a clear competitive advantage for the promoted project. Financing is almost impossible to obtain if the firm does not own the intellectual property rights to the promoted project.

- Quality science and technology

The vast majority of capital supply siders agree that the quality of science is very good in Canada. Very good ideas and very good science come from all Canadian universities. The U.S. obviously has more scale, a factor of about ten times, but Canada definitely has some leading cutting-edge technologies. According to a few interviewees, productivity in terms of product development and relative weight of R&D activities conducted in the Canadian research facilities of the big pharmaceutical companies confirms the credibility of Canadian science. Some companies spend as much as 10% of their R&D expenditures in Canada, although the Canadian share of the global market is only 2%. For these interviewees, this relative over-weighting of the Canadian share of R&D expenditures constitutes a direct validation of the quality of Canadian science. In R&D activities, Canada is seen as being very competitive. Without a more probing analysis, this may be related to a weak Canadian dollar and not to a real productivity or comparative advantage.

Other interviewees stress that in spite of the high credibility of Canadian science, not many Canadian firms have a dominant position in terms of size and pipeline development. Some U.S. VC capital supply siders feel that Canadian firms have a lower quality of science and technology compared to U.S. firms, even if they believe that the quality of the scientists is probably comparable. These perception differences might be explained partly by the fact that other important determinants are at play during each stage of development. Quality of science does not necessarily mean that the critical mass of talent is available. For example, moving a firm to the Boston area might make sense from a critical mass point of view in that shopping for additional talent for expansion may be easier in this new setting.

Although science and technology rarely constitute a problem as such, they are important criteria in project evaluation and rejection, especially in connection with the depth of the

market (the so-called technology-market couple). Even when the technology addresses real medical needs, the market niche is often too small.

Although most interviewees agree that the quality of science is not a problem in Canada, at least two observations are advanced about this important financing issue. First, many venture capital firms are actively looking for the best projects at the discovery phase. Most of the time, they are pre-selecting the most potentially interesting projects at the very early stages of their development. These capital supply siders have the capability to handle the science issue and their rejection rate is very high if we consider early phase projects. Specifically, more than nine projects out of ten asking for financing are rejected. Put differently, the quality of science is not a financing issue at the venture capital level because it has been handled properly by the other capital supply siders working at the discovery phase (seed and pre-seed) and by the venture capital firms themselves. The interviewees at the discovery phase mention that the quality of science is an important problem at the very early stages of development. The evaluation of the potential commercial value of the science being developed represents, quite naturally, the biggest issue at later stages of development.

The second observation put forward by some interviewees is that the technology pool in Canada is wearing thin, and that some time might be necessary to regenerate the quality of the technologies in the reservoir. For them, the best technologies are already financed and few good technologies are available to be financed. Even if this point of view is not unanimously shared, a few capital supply siders express serious doubt about Canada's capacity to keep up the pace. This observation is important because, as we will see later, the vast majority of the interviewed venture capital firms clearly express an intention to invest more and more abroad in the coming years (mainly in the U.S. and in Europe). Only state-linked or labour-owned institutional capital supply siders do not express such intentions, probably because they are not allowed to invest abroad. However, they do represent an important player given their high level of investment in Canadian biotech projects.

Other important investment determinants, such as the liquidity of Canadian financial markets and diversification considerations, might explain this increased emphasis to invest in foreign technology. Whether these intentions should be considered as being purely hypothetical possibilities, or as real and potentially threatening determinants, is open to discussion. However, if intentions were realized, then such a major erosion of the technology pool of capital would certainly constitute an aggravating factor.

Three or four principles are at play with regard to the decision to invest in a project. They are technological advance, market, management and intellectual property. Thus, although the quality of science is an important factor, it is far from being sufficient for a "go" investment decision.

- Management team with a record of successful commercialization

Most capital supply siders consider that the management team, together with technology and market, are the major issues when they analyze a company. Management is considered as being at least as important as technology. Capital supply siders consider lack of management as being one of the major difficulties in Canada not only in terms of limited numbers of good managers, but also in terms of the extent and variety of experiences and skills. A few cases of recycled management are emerging where someone decides to move on and start another venture. They generally do a better job during the second and third times than they did during the first round. A majority of capital supply siders mention that hiring a CEO abroad is often a necessity in spite of the difficulties involved. For a few capital supply siders, the relative scarcity of good management teams in Canada is not a major issue since many Canadian firms are already prepared to face difficulties in this respect.

Although the situation is improving, lack of management will probably continue to be one of the biggest issues in investing in biotech companies in the near future. Because of

the protracted life cycle of a biotech company, a long period of time elapses without generating management. There are no mentors and managers basically have to come up through the ranks. The managers can be recycled in the community later, but Canada is still going through the first generation of on-the-job management training. We have some good management talent in Canada. There are VCs who do not have any problem finding good quality management teams and are happy with the people involved. However, there are not enough good managers for all the companies that currently exist and many interviewees state that they usually have to recruit some managers from either the U.S. or Europe. The latter is very difficult and costly.

When looking at possible investments, capital supply siders want these companies to be world-class; that is, companies that can compete with the U.S. in terms of technology, money and management talent. Other biotech companies, such as the big pharmaceutical companies, have ready access to more financial resources. Management has to build the business model, has to establish strategic partnership relations, and has to raise financing. The better management is, the easier it is to raise considerable funds, which in turn makes scaling up easier.

Finding a world-class CEO can cost significant amounts of money and take a long time; nine to twelve months is not uncommon. If the CEO comes from the U.S., the salary must be competitive. On average, the salary prior to adjustment for exchange rate and tax differences tends to be a little higher than that of a Canadian CEO. The adjusted salary tends to be a large figure. When a Canadian company first initiates a search, it has to be prepared to offer a package that may be three to five hundred thousand dollars.

A related problem is that good CEOs want to position themselves with firms that possess market capitalization in the 100 to 300 million dollars (CAN$) range. Small biotech firms therefore have a hard time, given their limited financial means, in being

competitive for top management talent. In Canada, the number of firms in this range of capitalization is limited compared to that in the U.S.

Management needs to cover a wide variety of skills, and different types of managers are needed. Most firms need a multi-disciplinary team, which covers financial management and planning, marketing, commercialization and strategic planning. The interviewees unanimously consider that lack of sales and marketing skills is a major problem in Canada. In this respect, Canada lacks the human resources who know how to establish the potential of a given market as well as how to exploit it. These kinds of skills matter greatly for small and new firms. These firms are often not able to adopt a direct commercialization strategy and have to adopt a licensing mode or strategy. This difficulty is complicated by the fact that the choice of the most appropriate strategy has to be made early in the strategic planning of the firm. Depending on this choice, very different human resources and approaches are needed. A direct link exists between firm size and quality of the management team. Hence, the quality of management hinders a more important and fundamental size issue—that there are too many small firms in Canada relative to the U.S. Furthermore, even if size does not directly alter the quality of science, it is a complicating factor. The quality of management is even more important than the quality of science for it is harder to move from pre-start-up to start-up and IPO. U.S. VCs perceive Canadian management teams as not being as qualified as those in the U.S. Though not specific to Canada, this is perceived as an important issue. For these VCs, quality of management is based on managers who have long experience in the business and the business is successful. It is easier to find managers with success in the biotech industry in the U.S. than in Canada. As for the quality of science, a kind of critical mass disadvantage to investment in Canada exists from the perspective of a U.S. VC. Nevertheless, these factors may not be decisive in the decision of these capital supply siders to invest in Canadian biotech firms. As seen below, factors that might play a more decisive role include existing opportunities in the local market, locus of control and time needed to supervise their investments, bigger relative size of U.S. firms, and

better liquidity of U.S. capital markets. These last two factors are becoming more important with the increase in size of many investment funds, and the risk inherent from non-domestic investment. Proximity is a very important consideration in the decision to invest for it directly affects the locus of control and supervision issues. The further away the investment is, the better its potential has to be. Moreover, some U.S. capital supply siders state that they will not invest unless strong capital support exists locally.

For many interviewees, the management problem in Canada arises because few CEOs in small and young Canadian biotech firms are trained in big pharmaceutical corporations, where managers would have been in-company entrepreneurs. Canada has a lack of experienced management, managers who have taken products through to market before. In Canada, few CEOs have gone through the full range of experience from development to clinical trials to product development, commercialization and manufacturing. An insufficient number of Canadian CEOs have this variety of experience. Moreover, the CEOs who work in the Canadian branches of big international pharmaceutical companies usually have more limited experience than an American CEO. Most of the time, the former CEOs have just done Canadian marketing or phase 4 experiences, and they have not experienced the difficulties over the full range of clinical trials from phases 1 through 4. Stated differently, the level of maturity of management in Canada might not reach the level that exists in the U.S. This appears to be particularly the case, for example, for the capacity to achieve good market positioning, to make market opportunity assessments, and to select the appropriate niche.

Strategic development that is well adapted to the market is crucial. Many interviewees consider that we rarely see firms in Canada that posses this capacity for good competition analysis early enough to efficiently reduce risk by adopting such a strategy. For the last five to six years, the substantial growth in biotech firms has increased the need for good management.

Despite this fast growth, many capital supply siders consider the situation as improving at all levels, even if many firms could improve their board. Board competencies are an important issue for they impact directly on the scientific and development strategies. However, there is still a lack of important specific management resources. For example, development is seen as one important issue. Canadian firms are in need of personnel that can establish close and personal links with the big pharmaceutical firms to develop contacts and promote strategic alliances. Lack of management in this respect appears more problematic as a company moves closer to development and pre-commercialization.

- Intellectual property according to the number and the quality of the patents held

Intellectual property, which is carefully reviewed before investment, is a very important issue for the investor. Intellectual property is not seen either as a problem or as a Canada-specific issue by the interviewees. Many patent agents specialize in biotechnology IP. Even young biotech companies realize early in their lives that they have to partner with leading law firms or intellectual property firms to protect their patents.

Even if IP is not problematic, most interviewed capital supply siders said they are more comfortable using U.S. law firms because they have more experience and they know their way around biotechnology. From the diligence standpoint, these interviewees are more likely to use the U.S. firms. The U.S. law firms are usually more strategically focused, and they actually map out the strategy to be implemented, and specify what the client should be aware of.

Canada has experienced a rapid evolution in IP policies during the last ten years. Prior to 1991, property laws were not seen as appropriate. Now IP protection is seen as being better. The IP culture is not yet seen as being as developed as that in the U.S. but the interviewees consider that progress is ongoing. Problems remain and Canada still lags to

a certain extent. For example, start-ups often come from the universities and better education about IP is needed at this level. IP issues become more complicated in the biotechnology sector because scientists like to publish, which allows them to earn money and become known. The problem is that sometimes they publish what is not protected. Since many Canadian firms are small and their personnel are relatively inexperienced, much is unknown about IP. A reluctance to share property rights and the fear to deal with big pharmaceutical firms are also sometimes a concern.

Thus, in Canada, IP is not a quantitative issue (there are competencies in Canada) but a qualitative issue. The difference becomes obvious when it comes to integrating intellectual property into corporate strategy. According to a number of interviewees, Canada often lacks the ability to devise and introduce a vision of IP, as well as a strategy for its development and valuation. To illustrate, the quality of patent agents and experts in developing IP strategies is inferior in Canada compared to other countries. Probably, the level of diligence put into IP could be greater. This probably reflects less sophistication in Canada generally on the selection of an IP strategy using offensive and defensive techniques.

- Scientific due diligence procedures

This dimension is not seen as an issue in Canada. But many capital supply siders rely on a North American network for their scientific due diligence. While due diligence procedures are good in general, their quality can vary from one situation to another. For example, at the private placement and institutional investor levels, the quality of due diligence procedures varies depending on the managers and the resources available. The more experienced funds in biotech do have deep scientific due diligence procedures, while the others find it harder to justify analysts to support the manager. In the latter situation, the manager is a generalist who relies on outside study.

- Major reasons for not providing funding for a project/stage

Most interviewees cite the lack of management depth and breadth as the major reason for not providing financing. Management inability to articulate what they are doing and to prepare professional business plans with workable topics is a second (and perhaps as important) reason not to provide funding. Very unrealistic expectations and even complete naiveté on the part of management about dealing with capital markets occurs. Many of these companies do not know how to be a public company and how to deal with investors and investments. Some capital supply siders believe that this also applies to some groups investing in biotechnologies as they learn by doing.

Limited breadth of the technology and/or limited market opportunities are other major reasons for not providing funding. Even if the capital demand sider has the best management team, it will not be able to add any economic value if the technology and market are inferior. Most research activities never reach the final product stage. As the technology advances in the development process, it becomes easier to estimate potential risk, and to mitigate financing difficulties. U.S. firms have deeper and more advanced pipelines than Canadian firms, partly because biotechnology development has taken place earlier in the U.S. This difference should diminish over time as more compounds reach the later stages of development. Stakeholders, like the big pharmas, also tend to limit their alliances to their specialization fields. Since a relatively smaller number of therapeutic fields are being developed in the Canadian-based research facilities of the big pharmas, this becomes a complicating factor if a Canadian firm tries to fund a wide range of research activities. Since big pharma research activities are organized globally, a small Canadian-based firm might not have access to the proper network as easily as a comparable U.S. firm if its compound does not belong to the specialization fields already being developed in Canadian-based research facilities.

Increasing concentration and the creation of consortia are among the most important changes observed in the pharmaceutical industry over the last few years. Only four to

five major players have survived recent consolidation in the industry. R&D and capital needs and capabilities to commercialize products globally are the drivers of this very intense M&A activity. Assessing its impact on the funding of research activities, especially for (generally smaller) Canadian firms, is not easy. If bigger players become more eager for products, this will facilitate the relative decentralization of research activities. However, consolidation may make the development of world-scale Canadian firms more difficult since these firms will be more dependent on the international distribution network. If the capability to distribute compounds rapidly and efficiently on a global scale becomes more important, this could weaken the position of a small firm when negotiating an alliance or the sharing of intellectual property rights. These firms might see their bargaining position and potential opportunities negatively affected by the increased dependence on a more concentrated distribution network. Although the direction of the impact is uncertain, it is likely to be fairly important in the future.

Attracting the attention of U.S. investors is not easy for an average-size Canadian firm. While U.S. interviewees are exposed to approximately 600 to 800 hundred deals annually, they only conclude between five to ten deals a year. Since they prefer to be involved with their financed companies, geographic distance is a factor. As a result, these U.S. stakeholders need a strong local co-investor. However, they know few such local investors with a good track record of investing in successful companies in the U.S. Furthermore, they have a home bias if investment in the same technology is available domestically in the U.S. Given this home bias, a Canadian firm must be a superior investment opportunity to attract such a U.S. investor.

Aspects not related to firms or project-specific characteristics also affect the decision not to provide funding. The general investment climate and flavour of the moment are determinants of the decision to provide funding. For some capital supply siders, capital markets not only changed dramatically over the past five years but will also change even more because of what happened with the dot coms. Since capital markets now prefer to

fund more advanced stages of development, ideas no longer get funded. Firms have to show that a drug is not only viable, but that it will make money for someone. There is a shift to people demanding investments in firms that start making money very quickly in order to have early cash value. These investors believe that this signifies that the public market is becoming more sophisticated. Their general feeling is that the investment climate will enter a more conservative period of unknown length.

The exposure of U.S. stockholders to Canadian biotech investment is limited to the companies that deal with funds that invest in Canada or to firms that have approached U.S.-based big pharmaceutical firms to establish alliances with an international organization operating in a number of countries. These firms receive many proposals from Canada partly because they have a research base here. The second avenue of exposure to the Canadian biotech community is through conferences, such as the Bio Contact conferences.

Some U.S. capital supply siders believe that the level of Canadian innovativeness is, on average, a few months to a year or so behind that in the U.S., and that business models and concepts originating from Canada are models that have appeared earlier in the U.S. U.S. capital supply siders are talking with a number of very innovative Canadian firms because these firms have identified or are developing a very unique technology or drug candidate. These U.S. capital supply siders hold similar perceptions about intellectual property in Canada. On average, the ideas and concepts presented to them from Canadian entities are somewhat behind those presented by U.S. entities but comparable to those opportunities presented by European entities.

Periods of intense biotech financing occur in Canada. A three- to four-year quiet period followed a large number of financings in the mid-nineties. In late 1999 and 2000, a new wave of biotech financings occurred. Thus, biotech financing is facilitated during "hot" financial markets and the boom part of the general economy cycle.

3.3.2 PERCEPTIONS OF RISK AND RETURN

Differences in perceptions between project promoters and suppliers of capital about future performance and risk are important determinants in the probability of obtaining financing. The VCs note that most firms believe that they can get to market or to some other target quicker than they actually can. The project promoters underestimate time and cost (i.e., actual time is twice as long and actual cost is three times as much).

The unpredictability inherent in the biotech sector is an issue. Capital supply siders with a long history of investment in biotechnology know the inherent risk of early stage technology companies. These investors believe that they will benefit from financing this sector by taking a long-term perspective.

The gestation time and time to get products (or drugs) to market is linked both to the sector and the quality of management. Long gestation times and missed targets for deliverables cause difficulties in stakeholder relationships with promoters due to their adverse impact on valuations. This is especially a problem in the bio-pharmaceutical segment, which is so highly regulated.

Differences in perceptions about risk and return in the negotiation process between firms and investors are an issue. An entrepreneur usually thinks his or her company is worth a lot more than what capital supply siders think it is. In general, the earlier the development stage of the company, and the less experienced management is, the wider is the value perception gap between the two parties involved. At least in the earlier development stages, promoters have poor knowledge about venture capital dealings.

Negative attitudes on both sides of a financing negotiation also play a role. Some capital supply siders admit that some venture capital groups advance term sheets that are too harsh, impose their terms and ask for as much as 60% of the company. Some firm CEOs have the attitude that capital markets are there to be used and abused, and exist only for their convenience. They try to get every last penny that they can for their shares, and they do not care if new shareholders make money or not. Most capital demand siders understand that investors take significant risks for which they deserve an adequate return as compensation for such risk bearing.

From the viewpoint of investment bankers, it is important that promoters become aware of the expected rate of return required by investors, and about the network value these investors bring to a project. Investment in biotechnology stock is associated with buying a lottery ticket by many financial analysts. They consider biotech stocks as being the second highest risk after mining stocks. Other capital supply siders believe that many participants are still unaware of the time and high risk involved in bringing a product to market entry. The nature and importance of perception differences vary from one group of capital supply siders to another. Venture capitalists by nature consider themselves as being set up to take risk. Their perceptual differences with entrepreneurs are not about risk but about value. For other supply siders, perception differences arise from misunderstandings about investor expectations and/or competitive returns available from investment in other capital market sectors.

Lack of realism about the required market capitalization required, and the difficulties involved in successfully listing a stock on NASDAQ are also important issues. The market capitalization of the firm must be in the $300 to $400 million range to get the attention of U.S. financial analysts. This is a prerequisite to show that a firm has the potential and the market capitalization that are necessary to do a public round of financing on NASDAQ. Thus, a $50 million firm has a formidable task if it is to be ready for a NASDAQ listing within a three-year span.

According to some capital supply siders, the total misunderstanding of finance by promoters causes the problem. Many capital supply siders also consider that the Canadian financing environment is too institutional and too protected, when compared to the U.S. According to them, many entrepreneurs do not realize how tough conducting business is in such a capital-intensive industry.

Since the supply of capital differs by phase of development, this is likely to significantly affect the relationship between demanders and suppliers of capital. While many capital suppliers can finance the initial phases with relative ease, such is not the case for subsequent phases. The majority of the VCs invest less than $5 million, and up to $10 million in very exceptional situations (i.e., longstanding and well-performing projects not yet ready for public markets). However, even in the case a drug delivery system that costs relatively less, fifty million dollars in financing is needed. This level of financing is often difficult to find in Canadian financial markets. Even if the public distribution is fully subscribed, the net proceeds will only be thirty to forty million dollars and a financing shortfall remains. Thus, capital demand siders need to plan early for a follow-up equity distribution in the U.S. financial market. The U.S. market is very competitive with a great number of participants. The Canadian market provides important leverage for U.S. market entry by increasing the capitalization of the Canadian firm.

Private rounds in the range of $50 to $70 million are possible. With such funding, a firm can go to phase II clinical trials. However, to reach phase III, most interviewees believe that the firm needs to partner with a big pharmaceutical company.

Some interviewees attribute the differences in perceptions of risk and return between promoters and investors to the small number of fund managers in Canada. They perceive these managers as not being very experienced due to the limited number of successes to date in Canada, although these fund managers are becoming more educated in the length

of time that it takes to develop a compound. With increasing sophistication through experience, the Canadian fund managers will be able to invest in these companies at an earlier stage.

The situation in Canada is changing quickly. Five years ago, there were no companies with billion dollar market caps in the biotech field in Canada. Today, we have about five (Biovail, BioChem Pharma prior to purchase, QLT, Angiotech and MDS). A few capital supply siders predict that ten or fifteen firms of this size will exist within a year or two, which means that some investment decisions will have matured and more investors will become comfortable with the idea of bearing risk because they will see successes. With more successes and more companies with billion dollar market caps, the belief is that more investors will be prepared to bear more risk.

3.3.3 Difficulty in valuing biotech firms

- Valuation methods for various groups of capital suppliers

While some capital suppliers use formal valuation methods, others perceive valuation as being more of an artistic process, especially for projects at the very early stage. Some VCs use a detailed evaluation process starting with the firm's history, an evaluation of the management based on their past successes, and an assessment of the technology or products. The state of development of molecules, an estimate of the capital required, markets, level of competition, and a complete financial analysis of cash flows and pro forma financial statements complete the analysis. Risk analysis accounting for the terms of shareholder contracts, as well as agreements and subscriptions, is also performed.

Valuation is more difficult for biotech firms since a significant part of a biotech firm's value consists of intangible assets, and regulatory uncertainty. Regulatory authorities can modify their position at any time, adding costs and delay to the approval process. Clinical and development risk and the general competition landscape are difficult to

quantify since few comparables exist. Since value depends upon perceptions, an important gap can appear if concepts are not well explained or understood.

Analysts and investors examine an array of valuation factors such as management, science, intellectual property, markets, regulatory context, type of business model, and liquidity of the firm's stock. Poor market liquidity can translate into a loss of 10, 15, 20 or even 50% in value in one day if a large investor disposes of his shares. Value can vary by 30 to 40% depending on the clinical stage and business model involved.

Any valuation process is ultimately a judgment call whatever the evaluation process being used. Some analysts say they use a complex evaluation procedure with up to 30 or 45 items to determine a base risk-adjusted rate of return or discount factor, together with a weighting scheme for the various factors involved. For example, 30% is a minimum base rate of return for phase I. The existence of long-term plans (five years and over) is seen as an important aspect given the ten to fifteen year development process. Price earning ratios or revenue multiples are used only to value more mature firms. Existing comparables in the market are important to establish value and estimate risk. External validation of the technology also is a consideration. Due diligence and follow up by a VC, as well as an alliance with a big pharma, add comfort for investors. Many stakeholders stress the importance of remaining critical about these deals.

An alliance with a big pharma has risk. If the big pharma is acquired or merged, the joint arrangement for development may be shelved if it is no longer a core priority. Sometimes big pharmas want to maintain their earnings per share for they fear the reaction of analysts if their earnings growth rate falls below a given target. So there is pressure to finance R&D and develop molecules so that there is no direct impact on earnings per share.

Valuation methods are tailored to the stage of development. When a firm already has products in the commercialization phase, revenues or profit multiples are used. The

discounted cash flow method, where cash flows are properly adjusted for the risks inherent in the stage of development of the drug, is another method employed. If the perceived risk is high, a discount rate, of say 30% per year, is used. If the drug is only in phase 1 or in the pre-clinical phase, the expected success rate is low, at say 10%, and it could be 50% for a drug already in phase 2.

At the pre-start-up or start-up VC stages, the valuation method is more of an art than a science. Many capital suppliers mention that feelings about management and the negotiation process are significant determinants, and that too low of a price has a negative impact on the performance of the promoter. The most commonly used formal valuation method uses comparables. Since the valuation process is an inexact process, a 10% variation in the valuation obtained by a VC is considered to be normal.

One valuation method consists of choosing an exit scenario, which means determining what the company might be worth at an expected future exit date. Then, the initial value that provides a 40 or 45% return is calculated. Hybrid valuation methods also are used where discounted cash flows models are used for a five to ten year window, and a comparable valuation method is used for a 0 to five-year window.

In all cases, to ensure valuation is not a garbage-in, garbage-out process, assessment of the quality of the valuation inputs is critical. To determine valuation inputs, most analysts examine a combination of methods in their attempts to model the value of those products.

Some analysts arbitrarily select the discount rate depending on where the companies are in the development cycle. Some analysts use a multiple of the long bond rate or ten-year bond rate as a base discount rate and then add a premium depending on the stage of development. Some analysts determine what multiple the stock will trade at when it has earnings three years from now. Some analysts make a net present value assumption

about quality. This is based on the likelihood that the product will be developed based on an examination of the design of the research or trials, and the firm's key people. Thus, given the variation in data quality and valuation methods used, value estimates can vary substantially.

Analysts consider the clinical stage reached by the product when predicting its chances of making it through. On average, a clinical trial, or even a pre-clinical stage, constitutes the only basis for taking a risk.

The traditional valuation method for biotechnology is discounted cash flow. As companies approach maturity in terms of having a product to market, analysts focus more on price earnings ratios. Typical multiples are 20, 25, or 30 times earnings depending on where the firm is in the development spectrum. Valuations change based on sentiment but investors and analysts use discounted cash flows for longer investment horizons and price earnings ratios for shorter horizons. For some companies, the issue is what they think they are worth compared to what the market thinks they are worth.

The argument that Canadian valuations are lower than those in the U.S. is no longer considered to be true. One interviewee aptly stated this as follows:

> *It used to be that when you showed up with your green sheet, which is the document that you market with, and you have used U.S. comparables, they would state that we are not paying the premium because those are U.S. comparable companies. Now they fully expect to see U.S. comparables, and they accept the pricing of the U.S. comparables for Canadian companies.*

- How do their practices differ from other competitors both domestically and internationally?

Practices are similar to those of their competitors at least domestically. Capital demand siders often argue that Canadian VCs do not evaluate Canadian firms, as do American

VCs. Many reasons could explain this alleged difference if it exists. These include a less competitive structure for the VC offer, smaller capital amounts because of smaller average portfolios in Canada compared to the U.S., and differences in the quantity and quality of companies in the two countries. Some interviewed capital suppliers believe that similar enterprises are valued less in Canada than in the U.S. Although some Canadian entrepreneurs think that they should establish their firms in the U.S., many capital suppliers stress that most of these firms do not have the critical mass to be in the U.S. Furthermore, the Canadian company needs to be really different from what already exists in the U.S. to attract U.S. investment. The interviewees also note the lack of knowledge about Canadian firms. Furthermore, due to the sharp market downturn, many capital supplier siders have refused new investments because they are maintaining those already in progress. Capital supply capacities limit the amount of capital that can be invested in new and ongoing ventures. Some interviewees suggest that European funding may be a more viable option for Canadian firms since Europeans see Canada as a port of entry into the U.S.

The capital supply siders offer many interesting insights about the nature and practices of the VC industry in Canada. These comments concern primarily the lack of competition or excessive level of inbreeding in Canada, and the relative immaturity of the industry in Canada compared to the U.S. This is reflected in the mentality and culture of Canadian capital suppliers compared to their U.S. counterparts. Many capital supply siders believe that Canadian VCs have much to learn from the U.S. VC industry.

The interviewees highlight many problems in Canada in the financing process related to the maturity and culture of Canadian capital supply siders. They emphasize the negative influence of the overly great role played by institutional investors in such financing, and the relative lack of maturity and realistic expectations of Canadian entrepreneurs. Many capital supply siders also stress the relatively few numbers of "real" risk capital groups in Canada.

Capital supply and demand siders share the perception that competition is lacking in Canada compared to the U.S. Canada has many players but no competitive spirit. Over the long-term, this will result in many unsatisfied investors in Canada. In the U.S., the many (generally private) players are creating capital pools (like BioCapital) to manage their investments. These investors see a need for more private players on the supply side in Canada for all the rounds from start-up through pre-IPO. In Canada, not many public firms have the level of market capitalization that is of interest to institutional investors. Since many IPOs by Canadian firms were premature, Canada has a number of firms with market caps that are too low. Some capital supply siders consider that these public firms do not have the necessary liquidity to progress and to give the return that is expected by investors. These public investors have expected holding periods of one to three years over which they want to earn expected returns through growth in market cap per share. While many of these interviewees perceive NASDAQ as a superior trade venue, a firm needs a market cap of over $500 million to do so. Such a market cap is usually attained when the firm has products on the market, and the firm needs capital to bring its products to market. If a firm succeeds in consolidating technologies and growth by finding partners, then it might be possible to list on NASDAQ. Otherwise, a firm might be in a liquidity crisis that can last for three to five years. Firms are vulnerable to stock market volatility when their shares do not have liquidity. Some capital supply siders believe that the TSX does not have the appropriate liquidity, contrary to their previous beliefs. So they are questioning whether listing on the TSX is still a good step prior to listing on NASDAQ. This will remove an important step in the necessary progression for institutional investors who are looking for investments with market caps of over US$500 million.

The development of the private risk capital industry in Canada is seen as a necessary and important development. Indirect sources of capital, such as Canadian pension funds, are perceived as having a very poor knowledge of bio-industries. Furthermore, two important factors seriously impinge on their capacity and willingness to invest in

biotechnology.

The first is the liquidity of the Canadian financial market, where most public biotech companies have relatively small capitalizations (below $500 million CAN). For many capital supply siders, lack of liquidity is an important issue for even solid and profitable Canadian biotech firms. The rapidly growing Canadian institutional investors are not interested in deals of seven (or even ten) million dollars. A purchase of 25 million shares of Axcan (or even Hemosol) represents 30% of the firm. Thus, players that could become more sophisticated investors in biotech do not want involvement in small capitalization investments.

Big pension and mutual funds want returns and are looking for safe and liquid value. Generally, they are increasing their relative allocation to non-domestic investments. They have no interest in significant exposure to small cap biotechs for they do not want to hold more than 10% of any one stock. Small investments demand too much supervision and management, and one manager cannot follow 40 to 50 stocks. A lack of portfolio managers also means that the number of stocks under management must be small. Some capital supply siders believe that more funds like BioCapital would be launched if more qualified and experienced small fund managers were available. Also, it is not reasonable to expect that investors will remain captive in a given fund or category of funds for more than two years. According to the interviewees, if no specific and effective government measures are implemented to invest in small cap biotechs, consolidations will continue to occur.

Some firms go public prematurely. VCs have financed few firms close to a 500 million dollar market cap. Capital supply siders believe this will not happen for the next generation of firms, and institutional involvement will be necessary.

- When funding in stages, what is the timing and the amount of each portion?

Financing in stages is not seen as being as important as expected. The attitude of VCs towards stage (tranche) financing has evolved somewhat. In the early stage, they try to limit themselves to only two portions, 60% of the amount being disbursed in the first payment since liquidity needs are usually higher. In contrast, the achievement of milestones is seen as being essential for investors who monitor their investments closely.

3.3.4 LEVEL OF OWNER COMMITMENT AND FINANCIAL PARTICIPATION IN THE PROJECT

While it is often seen as relevant in other sectors of activity, financial commitment from the promoters does not play any role in biotech financing. We hypothesize that since the financial means of most individuals are relatively small in such a capital-intensive industry, this traditional criterion does not provide any credible indication of project success.

3.3.5 DISCLOSURE OF INFORMATION

While the VCs rarely see disclosure of information as an issue, this dimension is seen to be a major problem from the viewpoint of the financial markets. Disclosure of information, for example, about product development, and clinical trial research design and results are essential inputs used by analysts to determine value. Although many biotech firms do not have a communication strategy aimed at the financial market, this deficiency is not perceived as being unique to the biotech industry.

3.3.6 STRATEGIC ALLIANCES AND MERGERS & ACQUISITIONS

The capital supply siders consider strategic alliances and mergers as important strategies, and believe that the current trend to their use continues to be strong.

Strategic alliances are critical because it is very rare that a company can be funded through to commercialization without bringing in a partner. Furthermore, the bigger pharmaceutical companies can bring in valuable technical expertise for building large plants, manufacturing and marketing. Generally, no international sales force needs to be established.

While VCs consider alliances, mergers and acquisitions as essential strategies, they acknowledge that they are difficult to accomplish. Alliances can occur at any stage of development of a firm with the exception of start-up. An alliance or partnership for basic research is usually narrow and specific, and more meaningful arrangements usually occur at more advanced development stages when there is a potential therapeutic candidate. Big pharmaceutical company alliance decisions are generally taken in a global perspective. Specific expertise fields play a critical role in this respect. The Canadian-based research centres of the major pharmaceutical firms do have alliances with biotech firms worldwide. Given the scale of their research activities, some research centres have more than 300 researchers involved in basic research. Firms are sometimes too small to be of interest for a big strategic partner. When the alliance occurs too early, it might be sub-optimal from a value creation viewpoint both for the firm and its stockholders. For some interviewees, strategic alliances are the link between phases 2 and 3. This link brings comfort to the financial market.

Many alliances are just window dressing for there is no substantial involvement from the big partner, and no real risk taking. The smaller firm receives little or no money, and the transaction is essentially risk-free for the Big Brother.

VCs follow two development models. The first model brings foreign firms to establish a lab or a facility in Canada directly or via a joint venture. The other model opts for VC participation in a small firm to strengthen its bargaining position in negotiation with a big potential partner. The VCs also may provide direct support in the form of expertise

in these instances. Whether or not the VCs can facilitate alliances through financial or tactical means is unresolved.

Alliances are seen as a positive validation of the technology of the smaller partner, especially when the alliance is with a big pharmaceutical company. Alliances are signals that convey credibility to financial markets. One problem with alliances is that sometimes stakeholders like VCs or financial analysts cannot speak directly with the big pharmaceutical partners because of confidentiality. This makes evaluating the alliance deal more difficult, and hampers the process of signalling its value to investors.

Acquisition of a Canadian biotech firm by a foreign firm is not perceived as being a negative event per se. While mergers do not mean that research centres will move out of the country, they do imply that decision and management centres may no longer be in Canada. Canadian-based research activities might be exposed to downsizing later if additional acquisitions bring in similar capabilities. In spite of these potential problems, many capital supply siders consider consolidation as a must to achieve critical mass for Canadian firms that are relatively small. Consolidation is important because many capital supply siders believe that the standards to go public in terms of minimum market caps are becoming more stringent. However, consolidation does not solve all financing problems, especially when the combined burn rate still exceeds available combined financial resources.

Most interviewees in the M&A business state that the biggest issue usually is who is "driving the bus" after the companies combine. Some of the issues deal with aligning the interests of management with shareholders. If management is drawing a large salary and options annually in a fashion unrelated to firm performance, they may not care about the return to the common shareholders. They may even resist any merger attempt.

When specialists in alliances or acquisitions at the big pharmaceutical firms generally pass on evaluated opportunities, it is because expected costs exceed expected benefits.

In these situations, the technology is valued much higher by the firm than by the big pharma. Healthy biotech companies have good and sound financial backing from investors, and look to the pharmaceutical industry to realize the value of the technology they develop. Companies without solid financial backing try not only to realize the value of their technology but also to create or fund some of their ongoing activities through alliances. These firms see alliances as a way of financing, while it should be used primarily to get the maximum value out of their research development. For many interviewees from U.S. pharmaceutical firm alliances, biotech firms tend to inflate the value of the technology. In turn, they approach the big pharmaceutical firms prematurely with an unrealistic price tag. As a result, they do not capitalize on their opportunities. In other cases, the opportunity may not be interesting for technical reasons.

The biotech companies do not realize how their technology fits into the overall scope of the drug discovery, and that delivering a target is just the first of a large number of risks that the pharmaceutical company has to finance. The big pharmaceutical firms are not willing to pay enormous sums of money for the technology, but they are interested in technologies that help or reduce the risk of drug discovery, and improve efficiency and accelerate the drug discovery process. Pharmaceutical firms seem less comfortable than the VCs in revealing their goals with respect to target rates of return on their investments.

Many pharmaceutical firms have deliberately decided to avoid the valuation of technologies because they find such efforts to be very inefficient and inaccurate. The value of a technology is firm-specific since its value depends on how access to a given technology enables the firm to further its own development process. Big pharmas value a product-based biotech firm differently from a technology-based company that is helping pharmaceutical firms discover new drugs.

When pharmaceutical firms are involved in acquisitions, they concentrate first on the business opportunities it brings to the table. After assessing the business transaction, they evaluate the alliance transaction. This is aptly stated by one interviewee as follows:

> *We like to not muddy the situation, we want to make sure that we put the horse before the caddie, and that the reason for establishing the transaction is to enhance effectiveness in drug discovery.*

While non-public information about the nature and conditions of deals is unavailable, sources of information to evaluate the amount of money that might be coming into Canadian firms from alliances or acquisitions with the U.S.-based big pharmaceutical firms are available. Usually, specialists in the field use the U.S. figures with the implicit assumption that Canadian activities represent about 1/10 of the U.S. figures.

3.3.7 GOVERNMENT COMMITMENT AND GUARANTEES FOR MANAGING RISK

Few U.S. capital supply siders appear to possess any specific information about government commitment toward biotech firms in Canada, although they perceive that encouragement as being greater in Canada than in the U.S. The Canadian situation is perceived as being more like the European situation where government provides many incentives both at the state and federal levels, to help young biotech companies to get established. U.S. interviewees with knowledge about the existing programs in Canada state that they would be tempted to start a firm in Canada because of these incentives. They also stress that the Canadian government must place sufficient pressure on biotech companies so that only the best and most innovative companies get started. By removing the market's natural selection process, companies that may not survive in a competitive environment without government assistance may exist for a couple of years in a government-assisted environment. They acknowledge that, since Canada does not have

an infrastructure as extensive and as mature as the one available within the U.S., incentives are justified to some extent so that new Canadian biotech firms can compete.

Some capital supply siders do not know the various programs well or consider that the government does not promote these programs aggressively enough. Even those that are using all kinds of programs mention that similar (or as attractive programs) exist in others countries like Germany. For them, the program drivers are great management and scientists, and not government programs.

R&D tax credits are seen as an important determinant for high-tech companies locating in Canada. Since personal income tax rates are higher in Canada than in the U.S., the tax holiday for foreign nationals helps to alleviate the lack of management. While it is unclear whether these incentives are cost-effective from a global economic perspective, the industry takes advantage of these tax provisions. Some of the higher tax burden also is offset by the lower cost of living in Canada.

Some capital supply siders believe that having programs or fiscal measures that encourage both investment in the biotech sector at the retail level and help to develop broader knowledge would certainly be helpful. However, unless an effective screening process to qualify or pre-qualify eligible companies is in place before fiscal incentives are offered, such a program could put small investor money at risk. Such programs could have a big impact on the stock market if the weight of the biotech sector in the TSX index was to rise to, say 6%, from its current weight of about 3%. In that case, institutional investors could no longer ignore investment in the biotech sector.

Big investors have some difficulties with portfolio diversification if they only invest in Canadian biotechnology. Attracting foreign institutional capital to Canadian biotech firms could offset this. This is severely hampered by the relative lack of liquidity of the Canadian financial markets.

Capital supply siders consider that Canada has been extremely proactive but could be even more active and biotech-friendly. However, it is important that government be very selective about where to invest, and on how those investments are structured. It is important not to end up with 500 companies that are too small for IPOs, and that have no knowledge about how to obtain the next level of financing. These interviewees believe that Quebec has done the best job among the provinces in fostering biotechnology through incentives. B.C has a better record for fostering technologies at the universities, and this is something that Quebec can learn from B.C. While Ontario does not appear to have a coherent strategy, it remains strong partly because of its broader market. An important question not broached by the interviewees is the degree of cost-effectiveness of the various federal and provincial fiscal and tax programs.

3.3.8 OTHER RELEVANT DIMENSIONS

In accordance with the viewpoint of many capital demand siders, some capital supply siders believe that more competition in the venture capital market would be beneficial. Not only do relatively few pools of capital operate at the venture level but the competition between these groups appears to be relatively low.

Capital supply siders note that biotechnology has a relatively low rating in the Canadian financial market. This is expected to change as the relative weighting of the biotech sector in the TSX index increases further from its recent increase (from approximately 0.5% to 3 %).

Capital supply siders find that many Canadian companies do not meet a minimum level of capitalization and size of shareholding. Trading volumes are much lower for Canadian IPOs versus U.S. IPOs in the biotech field, probably because Canadian issues tend to be smaller at US$20 to 30 million compared to the typical U.S. IPOs, which averages US$75 million plus. If most issues are floated to institutional investors, there is

a real lack of liquidity. Probably only 25% of the $25 million (or about $7 million) is in retail hands. Most of the recent group of companies that went public are Montreal-based. They include firms such as NeuroChem, Nexia, ConjuChem, and Chirotech, that trade on average less than 10 thousand shares a day. Thus, venture capital investors at earlier stages in these companies cannot exit as expected if little liquidity exists in the market place. Thus, new potential Canadian IPOs are either thinking about waiting to go to U.S. markets or to do a bigger Canadian issue, or even doing a late-stage private round instead of the IPO.

Since lack of market liquidity is perceived as the number one problem in biotech financing, many interviewees feel that Canadian institutions should be educated to better support biotech companies earlier in the process so that they can replace the IPO financing round with a mezzanine round so that they have enough financial resources for the next stage of development. They could then postpone the timing of their IPO until their market cap and their valuations are such that they can float an issue whose secondary trading has liquidity.

Capital supply siders believe that a number of good VCs exist, and that for the most part they are Quebec-based. They feel that an insufficient number of dedicated biotech funds exist relative to the supply of biotech investment opportunities to create a level playing field for some biotech companies. They feel that this is especially the case for non-Quebec-based funds. Since the U.S. VCs recognize certain parts of Canada as containing expertise in biotech, more specialized U.S. biotech funds are investing or planning to invest in Canadian biotech companies.

A minority of the capital supply siders advocate that the long-term investment model used by Canadian VCs no longer applies to biotech investment. They consider the terms of funds that range between five to seven years as being too long. They stress that such a long holding period, even for an institution, is overly long. They consider the Canadian

mindset as being a lagged evolution of the U.S. mindset in biotech but not in industries that Canada is very good at. They predict that Canadian VCs will experience major problems since returns for the next two or three years will be flat. While the annual long-term return on venture capital is 16%, it has been 45% to 60% annually for the three years prior to 2001.

Most interviewees agree that it is preferable if companies can develop further using private capital before going public.

Some capital supply siders believe that VCs are concentrating more on companies that have reached phase II or phase III, and that it is harder to finance firms at the pre-clinical stages. In others words, these interviewees believe that VCs are becoming less risk-tolerant, although they know the area better and they are ready to assume these risks.

Table 3.2: Quotes of interviewed supply side stakeholders

1. Business development is the most critical of all management issues facing Canadian firms.	2. In Canada, a lot of firms probably went public long before they should have.
3. Each year at BioContact the entrepreneur meeting with the investment bankers and financial analysts is a reality check. Entrepreneurs are not aware of the hard reality of the financial market place.	4. The capital supply structure will have to undergo major changes. We have more and more firms going public that are stuck under a 500 million market capitalization.
5. Without a doubt, the majority of Canadian firms will be acquired by foreigners, be it European or American firms.	6. On Wall Street, there have been very few investment banks that invested in AgBio given the few private initiatives outside the large corporations.
7. GMOs, the whole issue around GMOs controversy is a real negative … whether they're involved with GMOs at all.	8. There is a lot of problems in Canada with the financing process of the firms. There is a lot of players, but no competitive spirit.
9. In nutraceutics, we are waiting for legislation that would confirm or validate the market. Nutraceuticals and cosmeceutics would expand if appropriate regulation can draw the line between real science products and miracle products.	10. The quality of management is the biggest problem when we are developing a firm. There is a diversified and important need for management people, mostly in the marketing and sales department in Canada and in Quebec, more specifically.
11. In plant biotechnology a few big firms can block most development for they hold all the patents.	12. Canadian small firm is often too small to be an interesting alliance partner or could be crunched by bigger foreign firms.
13. Things that are different between the Canadian and American firms? Poor management. Poor management.	14. Alliance strategy is an area where the Canadian firms are very weak in, extremely weak.
15. We invest in only one project out of twelve or sixteen (acceptation rate of 1/12 or 1/16).	16. The depth of liquidity of the markets in Canada is less, so that is a constraint. You don't have the capital access, you don't have the sophisticated investors, you don't have the ability to list, to get a proper valuation, financial analysts and so it begins to feed on itself.
17. One should not believe those who say that they are going to be ready for the NASDAQ in three years. Do you know that you will have to go from a market capitalization of 50 million to 400 million? Otherwise, financial analysts will not follow your company.	18. The single biggest problem is too many companies with not enough management and not enough breadth of technology. The perception in the U.S. is that there is a lot of "one trick ponies" and they're companies that are very thin on management. The technology may be excellent but it's not brought up to build up an entire company.
19. How early a company can go public depends on the current market sentiment. Right now it's exceptionally difficult to go public for most firms. Many of the companies that went public too early last year have seen their market value drop tremendously. So there is risk in going too early but market place acceptance changes all the time.	20. Very often it's a lack of depth and breadth of the management groups and perhaps as well, even of a complete naiveté on dealing with capital markets, for example. Many of these companies do not know how to be a public company. And even …dealing with investors and investments.
21. Liquidity is a huge issue for people. Many of the companies… And it is difficult to get the breadth of the share holding one would like. It would be a great benefit if companies could be driven further with private capital before having to expose themselves to the public market.	22. Some groups think that an IPO is liquidity. And you say no, IPO is not liquidity. Liquidity comes when you are a billion dollars and the new investors can make money on the IPO.
23. Given that the consolidation of the financial sector among the investors' funds has accelerated, it becomes	24. When we look at the company, we like what we see in Quebec or in British Columbia. Institutions want to be

progressively more difficult for those groups to look at smaller companies.	able to get in and out of stocks, buy and sell them quickly and without disrupting the market by their own activities. Therefore they want to invest in very large capitalization companies.
25. Critical mass is a huge issue, many of the companies have difficulty getting the critical mass and it's a moving target as we continue to see consolidation on the financial sector and the natural growth of funds. It's going to be a higher board for the company to get to the IPO stage.	26. And there are plenty of companies that are starving for capital here for good reasons. You don't have to be Canadian to have that issue.
27. An investor who's only interested in an economic return in biotech is looking for this 45 to 50% rate of return.	28. It's great that Merck is their partner because that means their science and their IP and everything must be good. But then the question is what is the cost? So you have to balance off the need for validation, which is extremely important and the cost of that.
29. The perception is that it's a lot easier for a very young company to get funded in Canada. But then the problem is what happens after. So there has to be consolidation because a lot of these companies can't move forward but yet you still see people kicking in a million or two.	30. I'm impressed with everything I've ever seen. I've been in conferences in Vancouver, Calgary, Montreal, and Toronto and always I'm impressed. I'm always surprised that the world doesn't know more about that.
31. And if the TSX and the European markets are sometimes distractions, it could be negative because you're getting a market that's not liquid and who wants to compete with a market that's not liquid.	32. Canadian companies that are funded are called science projects. That is for the sake of the science and they spend too little time building into a business.
33. I think that it probably reflects less sophistication in Canada generally in selecting intellectual property strategy and have real offensive and defensive techniques.	34. The whole project management is an issue.

CHAPTER 4

CAPITAL REQUIREMENTS FOR THE THERAPEUTICS SUB-SEGMENT OF THE CANADIAN BIOTECHNOLOGY INDUSTRY

The primary objective of this section is to estimate total capital requirements for the therapeutics sub-segment of the Canadian biotechnology industry using an improved estimation method, new data about development costs and attrition rates, and a more complete and updated state of the pipeline of molecules for Canadian therapeutics biotechnology firms. In addition, this section also provides initial estimates of the aggregate external capital requirements of our Canadian sample.

The capital requirement estimates are obtained from scenario analyses using input vectors for five exogenous variables: the aggregate number of molecules in development, potential growth of the aggregate pipeline of molecules, average time up to market entry, development costs, and failure (attrition) rates at each development stage. The purpose of the scenario-based analyses is to provide benchmarks over a mid-term (five-year) planning horizon, a period long enough to develop appropriate financing policies at firm and government levels. The scenario analyses quantify the sensitivities of capital requirement estimates to changes in the relevant input variables, especially the development cost and attrition rate vectors.

4.1 GENERAL METHODOLOGY FOR ESTIMATING CAPITAL REQUIREMENTS

The United States is an increasingly important segment of the world market for pharmaceutical products.[3] Since most Canadian firms want to sell their products in this dominant market, the development of a therapeutic molecule is highly influenced by the regulatory requirements of the U.S. Food and Drug Administration (FDA). This directly

[3] The United States is the world's largest market for pharmaceutical products, accounting for 48.2% of worldwide sales in 2000. In contrast, Europe and Japan represent 23.7% and 16.2%, respectively, of the world market in 2000 (IMS Health, 2001).

affects the development and testing costs of Canadian therapeutic firms. Since the review processes are very similar in Canada and the U.S., the development of a new drug typically follows the steps given in Table 4.1. Given the absence of Canadian data on development costs and attrition rates, the U.S. data are used herein.

Table 4.1. The development process for a pharmaceutical drug

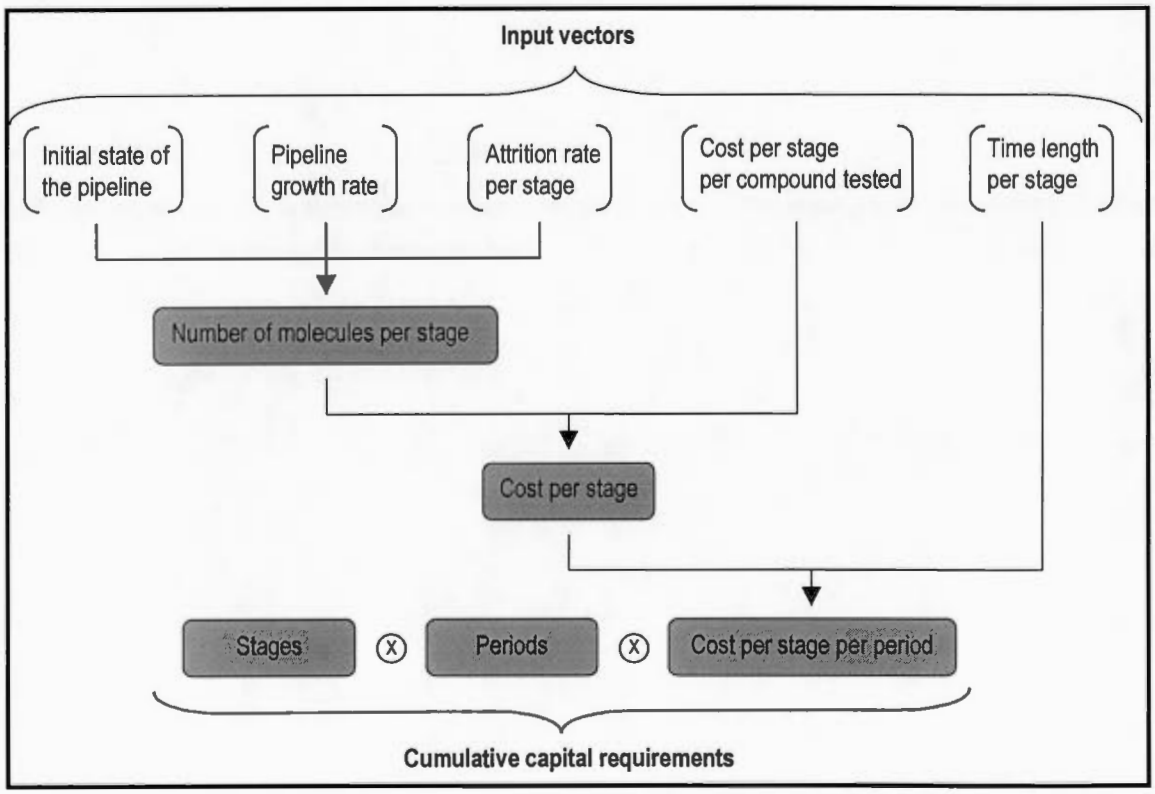
Development stage	**Early Research**	**Pre-clinical Testing**		**Clinical Trials**				**FDA**
				Phase I	**Phase II**	**Phase III**		
Test population		Laboratory and animal studies	IND filing at FDA[a]	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	NDA filing at FDA[b]	
Purpose	Discover a drug candidate	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, & look for side effects	Confirm effectiveness, & monitor adverse reactions		Review process and approval

[a]IND refers to Investigation New Drug. [b]NDA refers to New Drug Application.
Source: Spilker (1998).

Once a new compound is identified (discovery stage), the molecule enters laboratory and animal tests where the safety and the biological activity of the compound are studied (pre-clinical stage). After the filing of an Investigation New Drug (IND) application, the molecule is tested on humans. These clinical trials involve three phases. In Phase I, safety and dosage tests are conducted on a small number of usually healthy volunteers. Phase II extends the safety control on volunteer patients and assesses the efficacy of the drug. Phase III involves a large number of patients in order to statistically confirm efficacy and detect any side effects. The company then files for a New Drug Application (NDA). If the FDA approves the new compound, the company can begin to bring it to market.

The development process for a typical drug is very long, costly and risky. Thus, the method to estimate capital requirements, which is depicted in Figure 4.1, is based on various scenarios that capture these three features of the drug development process. The model accounts for the five development stages from pre-clinical testing to the review process. The discovery stage is excluded from the model because the number of molecules, failure rates and development costs cannot be estimated objectively for this development stage. While up to 5000 compounds per approved drug can be screened at this stage, there is usually no reliable public information about the number of molecules actually discovered and tested.

Figure 4.1. Capital requirement estimation procedure



The output of the estimation procedure used herein is the total amount of capital needed to bring existing and future molecules up to market entry. The model does not separate the capital required into its two major components, namely, internally and externally generated capital. An indirect procedure is used to obtain an estimate of total external capital requirements using those firms who have publicly indicated an interest in obtaining external financing.

We use various scenarios about the number of molecules in the pipeline with and without new molecule entry into the clinical testing stage of the development process. The scenarios, which assume that no new molecules enter the pipeline, are used to evaluate the capital required to bring to market only the compounds currently being developed within Canadian firms. The sensitivity of the capital requirement estimates to the cost and attrition rate assumptions is tested by using two different data sources, both with and without changes in R&D productivity. To assess the sensitivity of the outcomes to the number of molecules in the pipeline, we increase the initial number of molecules in the pre-clinical stage by 20%.

The more realistic scenarios allow for the entry of new molecules into the pre-clinical stage. All of these scenarios with new molecule entry assume that the number of new molecules entering the pipeline remains constant after 2006. The reason is that technological uncertainty is too high beyond this five-year planning horizon to make any meaningful projections of the subsequent rate of growth in new molecule entry. Different growth percentages are used to assess the sensitivity of the capital requirements to this determinant. Two data sources also are used to test the sensitivity of the capital requirement estimates to the development cost and failure rate assumptions used at each development stage. Input variables and their quantification are presented in Appendix A.

This estimation procedure has two potential limitations. The first potential limitation is that it uses aggregate input data. Durations, costs and failure rates differ across firms and therapeutic fields. However, an alternative methodology, which aggregates capital requirement estimates made at the individual firm level, may not generate better predictions. This alternative methodology imposes significant information-disclosure burdens on companies, is more costly to implement, and does not benefit from the typical error diversification effect achieved from increasing sample size. The second potential limitation is the quality of the input data, although the average durations of the different development stages often are quite similar across data sources.[4]

4.2 CAPITAL REQUIREMENT ESTIMATES5

In this sub-section, we present various capital requirement estimates based on the state of the Canadian pipeline in 2001 as reported in Table A.1 in Appendix A.

4.2.1 CAPITAL REQUIREMENT ESTIMATES USING SCENARIOS WITH NO NEW MOLECULE ENTRY

The capital requirement estimates for the four base case scenarios with no new molecule entry are reported in the second column of Table 4.2. Since no new molecules enter the development process in these scenarios, only the total cost of bringing the current Canadian pipeline of molecules to market is estimated. Since the average duration of the development process is 8.5 years, all molecules currently in the pipeline will have exited by the end of year 2010.

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[4] The average duration of each development stage usually varies within a range of plus or minus six months, except for the prior clinical test stage. In addition, some sources refer to the total discovery and pre-clinical testing stage, while other sources account only for the pre-clinical tests.

[5] All the values reported in this section are in Canadian dollars, although the input data tables (i.e. Tables A.2 and A.3 in appendix A) report U.S. dollars. A fixed exchange rate of 0.635 is used to translate U.S. into Canadian dollars. This corresponds to the mean FX rate at the end of October 2001.

Table 4.2 Estimates of the capital required to bring the current Canadian pipeline of molecules (Industry Canada pipeline 2001) up to market entry assuming no new molecule entry into the pre-clinical development stage

Scenario for development cost and attrition rate vectors[a]	Total capital required by 2010 (billions of CAN$)	
	Base case	20% increase in number of molecules in pre-clinical trials[b]
1	39.3	41.9 (+6.1%)
2	14.7	15.8 (+7.4%)
3	46.1	49.2 (+6.7%)
4	9.1	9.8 (+7.8%)

[a]Scenarios 1 and 2 use the development cost and attrition rate vectors before improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively. Scenarios 3 and 4 are the corresponding vectors after improvements in R&D productivity.

[b]The percentage change over the base case is reported in the parentheses.

These total capital requirement estimates differ substantially by the source of the cost and attrition rate vectors, and for the same source depending on whether or not the cost and attrition rate vectors reflect the impact of technological change. To illustrate, the capital requirement estimates using development cost and attrition rate vectors that are not adjusted for technological change that are obtained from PricewaterhouseCoopers and McKinsey are $39.3 billion and $14.7 billion, respectively. These estimates correspond to total costs per approved drug of $787 million and $359 million, respectively.

While both data sources are based on the expectation that the development cost per approved drug will decrease by about 25-30%, the direction of the change in the resultant capital requirement estimates depends on the data source used. Total capital requirement estimates increase by more than 17% when technological change impacts the cost and attrition rate vectors as envisioned by PricewaterhouseCoopers. In their methodology, the fall in the total cost per approved drug is more than offset by the increase in the individual cost per compound tested at every stage but the first (see Table 4.2). Moreover, while the cumulative attrition rate over the whole drug development process drops, this eventually leads to an increase in the number of molecules reaching

the market. In turn, more capital is required to develop these additional molecules that would have been eliminated during the previous process. In contrast, total capital requirement estimates decrease by 38% when technological change impacts the cost and attrition rate vectors as envisioned by McKinsey. Under the McKinsey methodology, the drop is due almost entirely to reductions in clinical development costs. While it is difficult to choose between these two contradictory views of the net impact of technological change on development costs, our initial capital requirement estimates suggest that the common belief that R&D productivity and capital requirements are positively related is suspect.

The sensitivity of the capital requirement estimates to changes in other important determinants depicted in Figure 4.1 is examined next. Based on the capital requirement estimates, which are presented in the last column of Table 4.2, a 20% increase in the number of molecules in pre-clinical trials (i.e., a 8.7% increase in the total number of molecules in the pipeline) increases the capital requirement estimates from 6.1% to 7.8% depending on the scenario examined.[6] Based on results not reported to save space, an increase in the duration of the total development process from 8.5 years to 11 years only increases the capital requirements marginally (by about 0.1%). Thus, as expected, the choice of development cost and attrition rate vectors appear to be the most important determinants of capital requirement estimates.

4.2.2 CAPITAL REQUIREMENT ESTIMATES ASSUMING NEW MOLECULE ENTRY INTO THE PRE-CLINICAL DEVELOPMENT STAGE

The capital requirement estimates for the aggregate pipeline of Canadian firms existing in 2001 for the four sets of scenarios with entry of new molecules are presented in Table 4.3 on a total and average annual basis over the entire period and over the first five

[6] The robustness of the estimation procedure is verified by increasing the number of molecules by 20% for each development stage. As expected, this, results in a 20% increase in expected capital requirements.

years.[7] Each set of scenarios includes five different rates of growth in the entry of new molecules into the pipeline over the next five years; namely, 0%, 10%, 15% (the base case), 20% and 30%. The 0% growth rate can be viewed as a pipeline (sample) with 1-for-1 molecule replacement as a molecule leaves the pre-clinical development stage. In contrast, the assumption in the previous section was 0-for-1 in that each molecule in the pre-clinical development stage is not replaced as that molecule migrates to the next development stage or fails. Similarly, a 15% growth rate signifies a 1.15-for-1 replacement rate, or that 1.15 molecules entry the pre-clinical development stage for each migrant from that development stage.

[7] Note that the capital requirement estimates do not account for the time value of money. Consequently, the yearly annual capital requirement estimate is simply obtained by dividing the cumulative estimates by the relevant number of years.

Table 4.3. Capital requirement estimates for the current Canadian pipeline of molecules (Industry Canada pipeline 2001) for various new molecule entry rates into the pre-clinical development stage

Scenario[a]	Growth rate (%) in new molecule entry (first 5 years)	Cumulative capital requirements (billions of CAN$)				Average annual for:	
		2001-2006	2006-2011	2011-2016	Total	Full 15 years	First 5 years
1	0	46.9	45.7	45.9	138.5	9.2	9.3
	10	48.9	62.1	73.2	184.1	12.3	9.8
	15	**49.9**	**72.3**	**91.0**	**213.3**	**14.2**	**10.0**
	20	51.1	84.0	112.2	247.4	16.5	10.2
	30	53.7	113.0	166.4	333.0	22.2	10.7
2	0	21.6	20.8	20.8	63.1	4.2	4.3
	10	23.0	29.5	33.4	86.0	5.7	4.6
	15	**23.8**	**35.1**	**41.7**	**100.6**	**6.7**	**4.8**
	20	24.7	41.5	51.5	117.7	7.8	4.9
	30	26.7	57.4	76.6	160.8	10.7	5.3
3	0	67.4	63.6	63.0	194.0	12.9	13.5
	10	73.0	90.3	100.5	263.8	17.6	14.6
	15	**76.3**	**107.3**	**125.0**	**308.5**	**20.6**	**15.3**
	20	79.8	127.1	154.0	360.9	24.1	16.0
	30	87.6	176.9	228.4	492.9	32.9	17.5
4	0	15.5	14.4	14.4	44.2	2.9	3.1
	10	16.9	21.0	23.1	61.0	4.1	3.4
	15	**17.7**	**25.3**	**28.8**	**71.7**	**4.8**	**3.5**
	20	18.5	30.2	35.6	84.4	5.6	3.7
	30	20.5	42.7	53.0	116.2	7.7	4.1

[a] Scenarios 1 and 2 use the development cost and attrition rate vectors before improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively. Scenarios 3 and 4 are the corresponding vectors after improvements in R&D productivity.

The corresponding estimates per stage of molecule development are presented in table 4.4 below for the fourth scenario.

Table 4.4 Scenario 4*: Breakdown of capital requirements per stage of development for various new molecule entry rates into the pre-clinical development stage

Growth rate in new molecule entry (first 5 years)	Development stage	Cumulative capital requirements (billions of CAN$)				Average annual for:	
		2001-2006	2006-2011	2011-2016	Total	Full 15 years	First 5 years
0 %	Pre-clinical	5.4	5.4	5.4	16.2	1.1	1.1
	Phase I	3.4	3.5	3.5	10.5	0.7	0.7
	Phase II	2.4	2.1	2.1	6.6	0.4	0.5
	Phase III	4.2	3.3	3.3	10.7	0.7	0.8
	Approval	0.1	0.1	0.1	0.3	0.02	0.02
10 %	Pre-clinical	6.5	8.6	8.7	23.8	1.6	1.3
	Phase I	3.7	5.4	5.6	14.8	1.0	0.7
	Phase II	2.4	3.0	3.4	8.8	0.6	0.5
	Phase III	4.2	3.9	5.2	13.3	0.9	0.8
	Approval	0.1	0.1	0.1	0.3	0.02	0.02
15 %	**Pre-clinical**	**7.1**	**10.7**	**10.8**	**28.7**	**1.9**	**1.4**
	Phase I	**3.9**	**6.6**	**7.0**	**17.5**	**1.2**	**0.8**
	Phase II	**2.4**	**3.5**	**4.3**	**10.2**	**0.7**	**0.5**
	Phase III	**4.2**	**4.3**	**6.5**	**15.0**	**1.0**	**0.8**
	Approval	**0.1**	**0.1**	**0.2**	**0.4**	**0.03**	**0.02**
20 %	Pre-clinical	7.8	13.2	13.4	34.4	2.3	1.6
	Phase I	4.0	8.0	8.7	20.7	1.4	0.8
	Phase II	2.4	4.2	5.3	11.9	0.8	0.5
	Phase III	4.2	4.7	8.0	16.9	1.1	0.8
	Approval	0.1	0.1	0.2	0.4	0.03	0.02
30 %	Pre-clinical	9.3	19.7	20.0	49.0	3.3	1.9
	Phase I	4.4	11.5	13.0	28.9	1.9	0.9
	Phase II	2.5	5.7	7.9	16.0	1.1	0.5
	Phase III	4.2	5.7	11.8	21.7	1.4	0.8
	Approval	0.1	0.1	0.3	0.5	0.03	0.02

* This scenario uses the development cost and attrition rate vector after improvements in R&D productivity obtained from McKinsey (Bhandari et al., 1999).

A comparison of the capital requirement estimates when only one determinant is allowed to vary at a time indicates that the annual, sub-period and total period capital requirement estimates differ substantially by the source of the cost and attrition rate vectors, by whether or not the cost and attrition rate vectors adjust for the expected impact of technological change, and on the choice of the expected rate of growth of new molecule entry into the Canadian pipeline of molecules. Thus, for the base case rate of a 15% growth in new molecule entry, the total capital requirement estimates range from $17.7 billion (scenario 4) to $76.3 billion (scenario 3) over the next five years, and from $71.7 (scenario 4) to $308.5 (scenario 3) over the entire 15-year estimation horizon. The corresponding average annual capital requirement estimates range from $4.8 billion (scenario 4) to $20.6 billion (scenario 3) over the next five years, and from $3.5 billion (scenario 4) to $15.3 billion (scenario 3) over the entire 15-year estimation horizon.

Doubling the growth rate of the number of molecules entering pre-clinical trials over the next five years from 15% to 30% increases the total capital requirement estimates by about 60% on average over the total time period, and by only about 13% on average over the next five years. Similarly, a comparison of the scenarios with 0% and 15% growth rates in molecule entry finds that capital requirement estimates for the higher growth rate are about 59% and 11% higher over the entire period and the first five years, respectively.

A comparison of the average annual capital requirements for each of the three five-year sub-periods indicates that the capital requirements are expected to be most acute during the five-year period 2006-2011. Due to the long duration of the drug development process, initial growth in the pipeline of molecules is captured with a lag.

One can argue that these capital expenditures are underestimated. If most companies incorporate the technological revolution in their new drug development process over the next five years, clinical testing expenditures will decrease but basic research and pre-

clinical testing expenditures will increase. However, firms will still incur large capital expenditures to complete clinical trials on drugs that were already under development. Both of these two capital expenditure enhancers would drive up the capital requirement estimates over the period, five to ten years hence.

The sensitivity of the capital requirement estimates for scenarios with new molecule entry to an increase of 2.5 years in the duration of the drug development process is examined next. This necessitates an increase in the estimation horizon by two years, or up to 2018.[8] Unlike the corresponding estimates for the scenarios with no new molecule entry, an increase of 2.5 years in the duration of the drug development process decreases total capital requirement estimates by 15% (see Table 4.4). Everything else held constant, the two-year extension in the estimation horizon is not sufficient to compensate for the fewer number of molecules that are developed by the end of the extended estimation horizon when the duration of the development process is 2.5 years longer.

[8] Total capital requirements are divided by 15 (and not by 17) to ensure the comparability of the estimates.

Table 4.5 Sensitivity of the capital requirement estimates for the current Canadian pipeline of molecules to various changes in development duration for various new molecule entry rates into the pre-clinical development stage

Scenario[a]	Growth rate (%) in new molecule entry (first 5 years)	Cumulative capital requirements, 2001-2018 (billions of CAN$)	
		Cumulative	Average annual
1	0	118.9	7.9
	15	**180.1**	**12.0**
	30	278.6	18.6
2	0	54.2	3.6
	15	**85.3**	**5.7**
	30	135.7	9.0
3	0	167.4	11.2
	15	**263.6**	**17.6**
	30	419.1	27.9
4	0	38.0	2.5
	15	**61.2**	**4.1**
	30	98.8	6.6

[a]Scenarios 1 and 2 use the development cost and attrition rate vectors before improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively. Scenarios 3 and 4 are the corresponding vectors after improvements in R&D productivity.

4.2.3 CAPITAL REQUIREMENT ESTIMATES FOR THE CANADIAN PIPELINE OF MOLECULES PUBLICLY SIGNALLING THE NEED FOR EXTERNAL FINANCING

As noted earlier, the total capital requirements for the pipeline of products for the sub-set of firms listed in the Recombinant Capital online database also are estimated. This estimate is used as a proxy of the total capital requirements that will need to be raised externally to finance development of the pipeline of molecules for the Canadian therapeutics sub-segment.

The capital requirement estimates for the aggregate pipeline of this sub-sample of Canadian firms for the four sets of scenarios with new molecule entry are presented in Table 4.5 on a total and average annual basis over the entire period and over the first

five years. While the total number of molecules in this restricted pipeline is about one-half of that in the full sample, the various capital requirement estimates for the base case growth rate of 15% in new molecule entry for this restricted pipeline of molecules is about one-third of those estimates for the full pipeline of molecules presented earlier in Table 4.2.

Table 4.6 Capital requirement estimates for the current Canadian pipeline of molecules publicly signalling the need for external financing (Recombinant Capital database 2001) for various new molecule entry rates into the pre-clinical development stage

Scenario[a]	Growth rate (%) in new molecule entry (first 5 years)	Cumulative capital requirements (billions of CAN$)				Average annual for:	
		2001-2006	2006-2011	2011-2016	Total	Full 15 years	First 5 years
1	0	19.5	12.4	12.1	43.9	2.9	3.9
	10	20.0	16.7	19.3	55.9	3.7	4.0
	15	**20.3**	**19.4**	**24.0**	**63.6**	**4.2**	**4.1**
	20	20.6	22.5	29.5	72.6	4.8	4.1
	30	21.3	30.1	43.8	95.1	6.3	4.3
2	0	8.2	5.5	5.5	19.2	1.3	1.6
	10	8.6	7.8	8.8	25.2	1.7	1.7
	15	**8.8**	**9.3**	**11.0**	**29.0**	**1.9**	**1.8**
	20	9.1	10.9	13.5	33.5	2.2	1.8
	30	9.6	15.1	20.2	44.9	3.0	1.9
3	0	25.5	17.5	16.6	59.6	4.0	5.1
	10	27.0	24.6	26.4	78.0	5.2	5.4
	15	**27.9**	**29.0**	**32.9**	**89.8**	**6.0**	**5.6**
	20	28.8	34.2	40.5	103.6	6.9	5.8
	30	30.9	47.3	60.1	138.3	9.2	6.2
4	0	5.6	3.8	3.8	13.2	0.9	1.1
	10	6.0	5.6	6.1	17.6	1.2	1.2
	15	**6.2**	**6.7**	**7.6**	**20.4**	**1.4**	**1.2**
	20	6.4	8.0	9.4	23.8	1.6	1.3
	30	6.9	11.3	13.9	32.1	2.1	1.4

[a]Scenarios 1 and 2 use the development cost and attrition rate vectors before improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively. Scenarios 3 and 4 are the corresponding vectors after improvements in R&D productivity.

4.3 CONCLUDING REMARKS

The capital requirement estimation method presented herein uses input data about molecule mix across stages, drug development costs, attrition rates, and development stage durations. This method is used to estimate the capital needs for various pipelines of molecules in the therapeutics sub-segment. These include the pipelines for all Canadian firms and all Canadian firms publicly signalling an interest in external financing.

The above analysis has two major findings. First, capital requirements are very sensitive to the chosen drug development cost and attrition rate vectors. Total capital requirements can be increased by a factor of 3 simply by using one data source over another, or by using vectors that account or do not account for the effects of technological changes and associated productivity gains on these input vectors. Second, whatever inputs are used, annual capital requirement estimates for the next five years represent several billon Canadian dollars. This implies a huge increase in capital requirements over amounts historically raised in the biotech sector during the recent past.

Even if our estimates overstate capital needs, since they assume that all molecules in the pipeline are actively being developed, these huge capital requirements should invoke a debate about whether or not financial markets have the capacity to finance the large number of molecules currently under development in the Canadian therapeutics sub-segment. Moreover, since our estimates show that technological changes do not necessarily reduce capital requirements, another interesting issue is whether the demand side of the drug market will accept to pay the price for tomorrow's medicine. Indeed, if a significant part of the molecules currently tested are introduced into the market, global healthcare budgets may grow significantly. If this is considered along with population ageing, the cost of tomorrow's medicine may be very difficult to bear. These results also raise a debate about the high level of regulation in the drug development process since

capital requirements are strongly and positively related to the stringency of the regulatory process.

Many issues are not accounted for in our capital requirement estimation procedure. For example, our procedure does not directly address the impact of the genomic revolution on the revenue structure of biotech firms. As it becomes harder to develop blockbusters, a lower market share is expected for each individual drug. Market saturation for therapeutic molecules may limit the economic incentives to develop new molecules. In turn, this may encourage a partial migration of development capacities towards other less regulated biotechnology segments or sub-segments, such as nutraceuticals or ag-biotech, with supposedly higher risk-adjusted prospects for profitability. This suggests that regulatory policy may have an uneven impact on the development of the various biotechnology segments, and especially on the relatively more regulated therapeutics sub-segment.

CHAPTER 5

CAPITAL POTENTIALLY AVAILABLE TO CANADIAN COMPANIES

Two main approaches are used to determine the capital potentially available to Canadian companies. The first approach is an empirical documentary approach that describes the amount of capital obtained by Canadian firms in recent years from each of the main sources of financing. The second approach uses a probabilistic model with various macroeconomic, market, and sector- and firm-specific variables.

5.1 EVALUATION OF RECENT CAPITAL SUPPLY TO CANADIAN BIOTECH FIRMS

In this section, we examine the amount of capital obtained by Canadian firms in recent years from each of the main sources of financing; namely, private investors and capital markets, investment in clinical research by large pharmaceutical companies, alliances, funds from Technology Partnership Canada (TPC), funds from Genome Canada programs, tax credits for research and development, and grants from different levels of government (federal and provincial). The data is obtained from various databases and press releases.[9]

5.1.1 MAIN FINANCING SOURCES

Capital for early stage and start-up firms comes primarily from public sources (research grants and other federal or provincial funding programs), various venture capital sources, and from alliances and joint ventures with large pharmaceutical companies. At the discovery phase, grants and tax incentives are often perceived as the most important sources of funding.

Later-stage companies with products in their pipelines have better access to capital from private investors and capital markets. These firms are actively engaged in pursuing

merger and acquisition (M&A) activities. Even if financing is not the main focus of these M&A strategies, they often help to preserve or improve present and future financing and liquidity.

Venture capitalists (VCs) play a pivotal role in driving the Canadian biotechnology industry. VCs are an important source of equity for start-up biotech firms. Canadian VCs are generally private partnerships or closely held corporations funded by private and public pension funds, corporations and institutional investors. Unlike the U.S., many Canadian VCs are government or labour-sponsored. The role of VCs is not limited only to providing funding. VCs generally are active investors, who guide, lead and nurture the companies they have invested in. Among the most well-known VCs in Canada are MDS Capital (the leading VC lender to the biotech sector in Canada), Ventures West, CDP Sofinov, and the Canadian Medical Discoveries Fund with capital under management of over $2.5 billion.

Institutional investors, corporations and banks also have pools of capital available for the Canadian biotech sector. They are important entities that seek to diversify their portfolios into this asset class. They invest directly or through affiliated subsidiaries. They are primarily concerned with expansion stage financing to attract a merger or acquisition with another company, or to enter the public market. Some institutional investors specialize in the acquisition, turnaround or recapitalization of public and private companies that represent favourable investment opportunities. They may have billions of dollars invested globally, and their primary objective is long-term capital appreciation. The most popular investors in this category in biotech are the Development Bank of Canada, CDP Capital, and the Royal Bank.

Another important source of capital for biotechnology companies are alliances and M&A activities. Big pharmas often fund a newer cash-deficient biotech company to do

[9] The main sources of data include Compustat, Recap, Contact Canada, Statistics Canada, BioCentury,

long-term risky research activities. For example, a recent alliance was formed between Vancouver-based QLT Inc. and Novartis Ophthalmic to perform a phase III clinical trial with a light-activated drug *Verteporfin*. This is a drug against skin cancer and other dermatological conditions first discovered by QLT. Novartis is financing the development of *Verteporfin* to a maximum of $15 million, and the two companies will share development costs beyond $15 million equally. The merger between Xenon Genetics Inc., a privately owned Vancouver-based clinical genomic company, and RGS Genome, a privately-owned Montreal-based clinical genomic company, brought together two leaders in the Canadian medical research industry to create a clinical genomic company that can compete internationally. Under the terms of the agreement, Xenon acquired all of the outstanding shares of RGS in exchange for cash and shares in Xenon. Xenon also established and funded a research centre in Montreal to further advance the research programs of the two companies.

Capital markets have also been an important source of financing for biotechnology in Canada. Canadian companies are accessing U.S. equity markets, and they commonly pursue dual listings in Canada and in the U.S. An IPO provides capital for companies as well as an incentive for VCs to invest in the company. Venture capitalists and owners of a firm seek to exit the investment within three to five years of their initial investment. The exit usually occurs through a merger or acquisition of the company by either the original founders or another company, or through an IPO. An IPO is considered as the most glamorous and visible type of exit.

In 2000, the most significant IPOs by Canadian biotech companies are Dynacare Inc. with net proceeds of US$46.4 million on the NASDAQ and the TSX, and CRYOCATH Technologies Inc. and Nexia Biotechnologies Inc. with net proceeds of $40 million each on the TSX.

Venture One, and MacDonald & Associates.

Federal and provincial governments develop initiatives to foster an environment in which biotechnology companies can succeed and grow. These initiatives address the specific needs of biotechnology companies, which include strong academic research institutions conducting basic research in the biosciences, access to early-stage capital, and a stable and supportive public policy structure. Generous tax incentives and grants have motivated many biotech companies to move to Canada. The most involved federal departments in biotech are: Industry Canada, Agriculture and Agri-Food Canada, Environment Canada, National Research Canada, Health Canada, Department of Foreign Affairs and International Trade (DFAIT), and Fisheries and Oceans Canada. The most involved agencies are: Genome Canada, Canadian Institutes of Health Research (CIHR), National Research Council (NRC), National Science and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council (SSHRC), and Canadian Food Inspection Agency (CFIA).

5.1.2 CAPITAL OBTAINED BY CANADIAN FIRMS FROM EACH OF THE MAIN SOURCES OF FINANCING

VENTURE CAPITAL

According to Macdonald & Associates, the life sciences industry raised $618 million from the Canadian VC industry in 2001 compared to $813 million in 2000. As shown in the table below, despite the decrease in the amount invested in the life sciences, the latter saw an increase of more than 1% from its 15.2% share of 2001.

Table 5.1 VC investments in Canada

Period	Life sciences in Canada (Millions of CAN$)	VC for all sectors in Canada (Millions of CAN$)	% of life sciences within total VC investments in Canada
1997	374	1647	22.7
1998	329	1528	21.6
1999	431	2637	16.4
2000	813	5337	15.2
2001	618	3732	16.6

PRIVATE INVESTMENT[10]

Institutional investors, corporations, banks, and mutual funds are important sources of capital for the biotech sector that mainly target later-stage companies. For 2001, the life sciences industry raised about $956 million. This amount is comparable to VC investment but is far above federal financing.

Financing from financial businesses, banks, insurance companies and other institutions is made mainly through equity, secondary offerings for existing public companies, convertible bonds, and through debt. For debt and new equity offerings, figures compiled by Dundee Securities Management Company are used.

ALLIANCES AND M&A

Biotech firms raise considerable capital through alliances, strategic acquisitions and mergers. Funds come from pharmaceutical companies that may be willing to replace the patents that are going to expire or simply want to acquire late-stage or marketed products to fill in their pipeline gaps in order to benefit from economies of scale or to expand their revenue bases. Funds also come from top-tier biotech firms looking to expand their capabilities by pooling resources with another biotech firm.

Private Canadian biotech companies can always approach public biotech firms and pharmaceutical companies for collaborations and equity injections. MethylGene, for example, has licensed the rights for its lead drug to MGI Pharma Inc. of Minneapolis for up to US$59 million. Caprion and Xenon each raised about $70 million in 2001 from partnership deals with Pfizer Inc., Johnson & Johnson, Sun Microsystems Inc. and Oracle Corp.

Even for public companies, alliances and M&As may be an interesting alternative for raising capital when faced with difficult capital markets or weak profits. This was the case of the Ottawa-based company, Adherex Technologies Inc. The company floated an initial public offering last June at a price of $1.50, but the stock price dropped in July after Shire Pharmaceuticals Group PLC walked away from an accord to develop Andherex's anti-cancer drug *Exherin*. The deal fell apart largely because Adherex was unwilling to share in development costs with Shire during the mid-year 2001 weakness in capital markets. The drug developer signed a new deal in October to develop its lead anti-cancer drug with the giant Astra Zeneca PLC.

Our estimates of the capital raised by Canadian biotech firms through alliances and M&As is based on U.S. data. Experts estimate that Canadian activities represent about 10% of the sector U.S. total alliances and M&A activities. This figure is consistent with that in the Pharmaceutical Industry Profile 2001, a report published by the PhRMA foundation.[11] This source reports that U.S.-owned research-based pharmaceutical companies spent US$451.2 million in Canada in 1999, or about 9.20% of their total R&D expenditures abroad.

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[10] Other than VC.

[11] Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2001, www.PhRMA.org .

Based on the 10% assumption, the estimate of capital raised by the Canadian biotech sector is about $182 million in 2000 and about $66 million in 2001.

IPOs

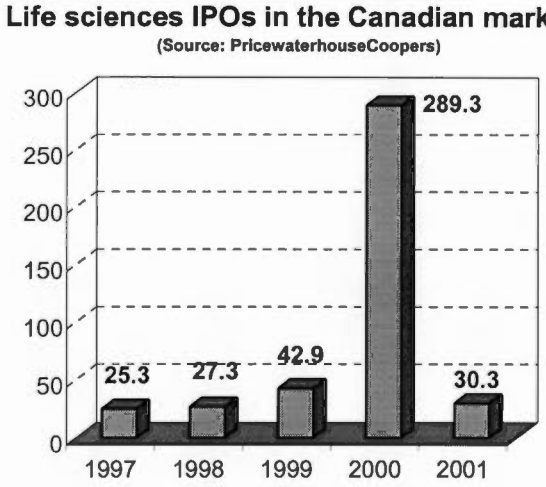
Biotech firms may consider an initial public offering for various reasons, such as to expand their businesses, improve market presence or to attract and retain staff and enhance the company's profile. Going public can be a pivotal step in the company's growth strategy. However, the current state of the financial market can seriously affect the capital that can be raised. Canadian biotechnology companies must be well-prepared to move quickly, and to get the IPO offering into the market when the market is receptive. Well-prepared business models, more investment savvy, and targeting specialist investors with a better understanding of the sector are all important considerations. When the market sector is hot, momentum buyers become active in the sector. While IPOs are a very important source of capital, they are subject to the "window of opportunity" phenomenon in capital raising.

The limited liquidity of the Canadian secondary market for initial offerings is an important issue. Firms must set realistic goals and create real opportunities for success that preferably do not depend on a single product or clinical trial.

According to a PricewaterhouseCoopers IPO survey for the year 2001, the gross value of IPOs in life sciences in Canadian markets declined 89.5% from its last year level. The average offer size and the number of IPOs also fell by 76.8% and 54.5% respectively.

As is evident from figure 5.1 below, 2000 was an unusually hectic year. The total gross value of all successful IPOs in the life sciences was $289.3 million compared to $42.9 million in 1999. The market behaviour observed in 2000 suggests that the window of opportunity for initial stock offerings can be short lived.

Figure 5.1 Successful IPOs in the life sciences industry in Canadian markets



GOVERNMENT FUNDING

According to the 2000 Statistics Canada Survey, the federal and provincial governments provided 6.4% of the funding for firms performing biotechnology R&D in 1999-2000. The estimate of $392 million for the period is an increase of about 22.7% over the 1998-1999 level of $319.5 million, and almost a 50% increase over the $262 million invested in 1997-1998. As shown in Table 5.2, as much as 97% of all expenditures are directed toward R&D activity. The remaining portion is directed toward related scientific activities, such as projects to support biotech businesses.

Table 5.2 Federal government science and technology (S&T) expenditures on biotechnology by activity and performer ($000s)

Activity/ Performer	Intramural[a]	Business Enterprise	Higher Education[b]	Performers		Total
				Foreign	Other[c]	
Panel A: 1999-2000						
R&D	177.855	34.577	164.521	628	1.922	379.503
Related scientific activities (RSA)	6.696	922	4638	250	-	12.506
Total Expenditures	**184.551**	**35.499**	**169.159**	**878**	**1.922**	**392.009**
Panel B: 1998-1999						
R&D	137.997	15.141	152.468	533	2.916	309.055
RSA	4.967	1.041	4.081	233	100	10.423
Total Expenditures	**142.964**	**16.182**	**156.549**	**766**	**3.016**	**319.477**
Panel C: 1997-1998						
R&D	113.074	6.379	132.142	507	1.612	253.714
RSA	3.425	980	3.634	230	10	8.279
Total Expenditures	**116.499**	**7.359**	**135.776**	**737**	**1.622**	**261.993**

[a]"Intramural activities" are inside federal government departments and agencies.
[b]The "Higher Education" sector includes universities, colleges and other post secondary institutions.
[c]"Other performers" include Canadian non-profit institutions and provincial and municipal governments.
Source: Statistics Canada, Biotechnology Scientific Activities in Selected Federal Government Departments and Agencies, 1999-2000, Catalogue 88-001-XIB, vol. 25, no3.

Based on Table 5.3, $185 million or 47% of the $392 million spent on science and technology in the biotechnology sector in 1999-2000 was spent within the federal government departments and its related agencies. The expenditures of the National Research Council (NRC) and Agriculture and Agrifood Canada are $103 million and $55 million, respectively. The remaining $27 million is spent by eight other government departments or related agencies.

Table 5.3 Federal government R&D expenditures on biotechnology activities by selected department or agency, and by performer, 1999-2000 ($000s)

Department/ Agency	Intramural[a]	Business Enterprise	Higher Education[b]	Performers		
				Foreign	Other[c]	Total
Agriculture and Agrifood Canada	55.479	-	-	-	-	55.479
Environment	572	435	342	-	40	1.389
Fisheries and Oceans	2.600	-	-	-	-	2.600
Health Canada	4.751	-	5	-	42	4.798
Industry Canada	3.324	29.354	55	-	-	32.914
Medical Research Council (now Canadian Institutes of Health Research or CIHR)	5.837	-	127.800	-	-	133.637
National Research Council	103.030	5.000	-	-	600	108.630
Natural Resources Canada	7.071	230	144	-	40	7.485
NSERC	1.800	300	39.900	800	1.200	44.000
SSHRC	86	-	914	78	-	1.078
Total Expenditures	**184.551**	**35.499**	**169.159**	**878**	**1.922**	**392.009**

[a]"Intramural activities" are inside federal government departments and agencies.
[b]The "Higher Education" sector includes universities, colleges and other post secondary institutions.
[c]"Other performers" includes Canadian non-profit institutions and Provincial and municipal governments.
Source: Statistics Canada, Biotechnology Scientific Activities in Selected Federal Government Departments and Agencies, 1999-2000, Catalogue 88-001-XIB, vol. 25, no3.

Higher education institutions are the second-largest beneficiaries of federal R&D expenditures in the biotechnology sector. These institutions account for $169 million or 43% of the total R&D expenditures by the federal government. These expenditures are mainly effected through the Canadian Institutes of Health Research (CIHR) and the National Sciences and Engineering Research Council (NSERC). Thus, higher education institutions receive 82% of the $207 million extramural spending by the federal government during 1999-2000.

Biotechnology firms received $35 million or 9% of the federal biotechnology expenditures in 1999-2000, with most of this funding being granted by Industry Canada. This department provided 90% of its $33 million in science and technology expenditures in the biotechnology sector directly to Canadian enterprises. Such expenditures more than doubled over the 1998/99-1999/2000 period, and do not include the $300 million allocated to Genome Canada.

Based on Table 5.3, the four major federal government fund distributors are the MRC (34%), NRC (28%), Agriculture and Agrifood Canada (14%) and NSERC (11%).

The annual values discussed on financing of the biotech sector in Canada by major funding source are summarized in Table 5.3 for the three-year period, 1999-2001.

Table 5.4 Financing in the Canadian biotech sector: An evaluation ($ million)

Year/Source	2001	2000	1999
Venture capital[a]	618	813	431
Private investments other than VC[b]	956.6	1178.4	1353.2
Alliances and M&A activity[c]	168.96	182.01	158.3
IPOs[d]	30.3	289.3	42.9
Federal government[e]	483.6	392	319.5

[a] MacDonald & Associates
[b] Canadian Health Care Financing Database - Dundee Securities
[c] Estimation based on 10% of U.S. alliance and M&A activities
[d] PricewaterhouseCoopers surveys on Initial Public Offerings in Life Science in Canada
[e] Estimation based on Statistics Canada data

We provide a description and a comparative analysis of the financial data of Canadian and U.S. public firms in Appendix B.

5.2 EVALUATION BASED ON A PROBABILISTIC MODEL FOR THE SUPPLY OF FUNDS

5.2.1 CONTEXT

There is no straightforward and simple method to estimate the capital available to Canadian biotech firms. Many factors can affect the amount of capital available from various sources, and past experience tends to demonstrate that many of these factors are subject to high volatility. Despite the inherent stochastic nature (random movements) of the fundamental factors affecting the supply of funds to any high-tech sector, robust models and methodologies do exist to establish the probability distributions that can properly describe or capture the supply generating process resulting from the complex interactions between the various relevant factors affecting supply. Obviously, the supply generating process will follow a stochastic process over time to a large extent.

Several stochastic models can be used to model the supply generating process. Thus, the first step is to determine the most appropriate model to start with. For example, one question that arises is whether the supply generating process follows a Markovian process, a "no-memory" process in the sense that future values do not depend on past values. Brownian motion and the Poisson process are two examples of this class of process. However, the so-called "Markov chain" type of models may better describe the supply generating process. A Markov chain has several states, all of which depend on certain other random variables. These other variables affect the change from one state to another. In biotech financing, there are several practical concerns depending on the source of financing. These include the experience of the investment manager that makes the decision, the valuation criteria used, and the other criteria used to make the financing decision. The choice of the specific model to be used in the analysis is based on

empirical testing and observed correlations between the relevant variables that are expected to be associated with the supply of capital to the biotech sector.

5.2.2 SELECTION AND BEHAVIOUR OF THE KEY VARIABLES AFFECTING THE SUPPLY OF FUNDS AND THE VALUATION PROCESS

This section identifies the relevant variables that are expected to affect the flows of funds to biotechnology companies. The choice of relevant variables is based on both the literature and an examination of the historical correlation matrix. Usually many variables are tested using historical data and then selected for the model, based on the goodness of the statistical fit obtained from the corresponding series of historic data. In this study, an alternative approach is used. We first try to identify a few key variables and then build a parsimonious model that incorporate these variables in order to produce future distributions of potential capital supply.

The key variables to be used in the model are the following:

- Two macroeconomic variables; namely: the level of economic growth and the level of interest rates in the Canadian economy;
- Market and sector variables, such as market risk premium, competitive industries returns and substitute products observed for other high-tech companies, returns of the biotech sector as a whole, past and forecasted, and perceived risk in the biotech technology markets, proxied by observed failure rates;
- Global availability of funds in recent years; and
- Firm-specific variables, such as average size and the size of the product development pipelines.

The levels of both economic growth and interest rates have clearly been identified as a significant and important determinant of the supply of risk capital in a free market economy. Therefore, it is an obvious choice (see, among others, Feen et al., 1995; Gompers et al., 1998 and 1999).

It is clear that competitive returns offered by the other high-tech sectors and substitute products may have an important influence on the supply of funds to the biotech sector. Basic economic reasoning suggests that the biotech sector has to be fairly competitive in order to attract risk capital, particularly when one considers the relatively longer product development time in this sector (especially in the therapeutics sub-segment) compared to other high-tech sectors. The failure rates observed in the biotechnology industry are also likely to be a key determinant of capital supply, for they proxy for the specific risks associated with biotech investments.

Global availability of funds also has to be considered for it defines the level of development reached by the Canadian venture capital industry and by other sources of capital used to finance a biotech firm.

The choice of the proposed firm-specific variables, though selected on a more ad hoc basis, tries to capture the evolution in the average stage of development of Canadian biotechnology firms. Stage of development is linked to the relative maturity of the product development pipelines of Canadian firms. Maturity of the pipelines is certainly a factor one should expect to have a significant impact on the perceived investment risk, and thus, on the evolution of capital supply through time.

The identification of the appropriate proxy for each variable and the characterization of the behaviour of the relevant variables are obtained by empirical and correlation analyses that try to replicate past behaviour of these variables.

In order to simulate the amount of capital available from the various sources, some kind of financial valuation model is necessary. Given the general characteristics of biotech firms, the use of traditional valuation models or techniques like the discounted dividend/cash flow model, price earnings, price to book or price to sales offer limited

possibilities. For example, holding shares of a biotech firm is a contingency claim on quite distant and hazardous revenues. Relatively long research and development periods (about 12 years for the important therapeutics sub-segment) combined with fairly high failure rates complicate any effort to estimate the parameters of the preceding models or techniques.

As we have seen in section 3.3.3, most investors are using a combination of methods together with the use of comparables. But given the nature of our simulation approach, the only valuation-related variable we need is the distribution of asset prices for the whole set of biotech firms. This comes from the fact that all the firms are in fact competing for the same dollar. This implicit hypothesis also can be applied to the whole set of high-tech firms. Hence, in the context of our simulation approach, the distribution of asset prices, is obtained through empirical modelling as will be shown later.

The identification and specification of the behaviour of the supply of funds is presented in the following section.

5.2.3 IDENTIFICATION AND SPECIFICATION OF THE SUPPLY OF FUNDS

The identification and specification of the supply of funds is performed through an empirical quantification of the parameters of the model described by equations (1) and (2) presented below. The empirical quantification of these parameters relies on the following steps:

- Determination of historical individual behaviour and their behaviours in relation to all others variables. This quantification is performed based on the specific historic database for each variable described in the preceding section;
- Determination of the actual state of each of the variables; and
- Simulation of the behaviour of each variable, as explicitly modeled by the equations presented in the next sub-section.

5.2.4 MODEL CONSTRUCTION AND CALIBRATION AND INITIAL VALUES OF THE KEY VARIABLES AND HYPOTHESES

a. Model construction and calibration

The purpose of the supply simulation model is to establish, within a certain level of confidence, the amount of capital that might be available to the Canadian biotech sector over the next five years. Although the simulation model presented below could be used to generate estimates over a longer time period, the statistical error of the corresponding estimates increases rapidly with the time span involved. A five-year period seems appropriate in light of the results obtained previously using the capital requirements estimation scenarios. Based on these results, the next five-year period seems the most critical in terms of potential growth in capital needs. Finally, given the high volatility that characterizes the biotech sector, a longer forecasting period would appear to be of limited use, since a five-year period is long enough to implement appropriate public and private-sector policies.

The estimation procedure presented in the following paragraphs is defined as a stochastic process. It simulates the amount of capital that might be available to the Canadian biotech sector based on a mathematical model that integrates the stochastic behaviour of each of the relevant variables introduced in sub-section 5.2.3 of the study. As noted earlier, these include interest rates, growth in the economy as a whole and in the biotech sector, as measured by the index of biotech companies and risk premium in capital markets. The interest rate policy adopted by the Central Bank has a direct impact on the availability of finds. For example, high interest rates tend to move capital away from the more risky investments. It is also well documented in the literature that economic growth has a direct and significant impact on the level of available risk capital. Changes in the biotech index and market risk premium are also important for they are proxies for investors' perceptions and market sentiment about return and risk.

Two main types of stochastic processes are used in the simulation depending on the variables chosen. These are a geometric Brownian motion and a mean-reverting stochastic process. The Brownian motion is used to simulate the random behaviour of the main financing sources whose initial states have been discussed earlier. For each variable, the behaviour of the governing stochastic process is limited to two parameters in order to keep the model parsimonious and tractable. They are defined next.

b. Brownian motion

In the case of the geometric Brownian motion, the following model is simulated:

$$dV_t = \mu V_t dt + \sigma V_t dB_t$$

where

- dV_t is the change in the random variable V at time t,
- μ is the drift in the random variable,
- V_t is the value that the random variable takes at time t,
- dt is the time interval between two steps in the simulation (herein, taken to be one month),
- σ is the volatility of the change in the random variable being simulated, and
- dB_t is the increment of the Brownian motion.

The Brownian motion is defined in the usual way, and with the following properties:

_ The process starts at zero, $B_0 = 0$,

_ B_t has stationary and independent increments,

_ The path of the Brownian motion is continuous,

_ The increments $B_t - B_s$ are normally distributed with mean equal to zero, and standard deviation equal to $\sqrt{t-s}$, so that:

$$(B_t - B_s) \sim N(0, t-s) \qquad for \qquad t \succ s$$

At each step of the simulation, we compute the new value of the stochastic variable as well as its increment.

c. Mean-reverting process

The other variables, which exhibit less erratic movements, are simulated using a *mean-reverting* process which is defined as :

$$dV_t = a(b - V_t)dt + \sigma dB_t$$

where:

- dV_t is the change in value, or the increment, of the random variable V_t,
- V_t is the value that the random variable takes at time t,
- a is the adjustment speed at which the mean reversion takes place (defined as one herein),
- b is the long-term value toward which the random variable V_t moves,

- dt is the length of time between two steps in the simulation,
- σ is the volatility factor, or the standard deviation of each of the variables considered in the model, and
- dB_t is the increment of the Brownian motion as described earlier

d. Initial values of the key variables and hypotheses

The initial values of the key variables and hypotheses used in the supply simulations are presented in Table 5.5. These values are used to simulate the potential supply of funds for the Canadian biotech sector. As mentioned earlier, two classes of variables are used, macroeconomic/sector variables, and financing source variables. Macroeconomic and sector variables are: the real interest rate, the growth rate of the Canadian economy, the TSX-biotech index growth rate, and a market sentiment variable (as proxied by the market risk premium). Financing source variables are private and public amounts of funding, and funding from the federal government.

Given the flexibility of the simulation program, both historical data and forecasts from existing public sources are used to select the initial values of industry and sector variables. For financing source variables, simple annual arithmetic means over the last three years, and over the last two years are also used (see Table 5.4 for data on past financings).

Monte Carlo simulations with geometric Brownian motion are used for the financing sources variables, and a mean reverting process is used for the macroeconomic and industry variables. A random shock multiplicative factor affecting only the private financing other than venture capital was introduced at a final step in order to account for the possible multi-period effect of the associated complex decision process for that specific funding source. This random shock factor does not affect the variable path but does amplify the variation dV_t, from one simulation to another.

In addition to the initial state of each variable, various hypotheses about the mean and volatility of the remaining variables are introduced, with the exception of private financing other than VC. Historical means and volatilities that are used in the simulation are reported in Table 5.5.

Table 5.5 Initial values of the key variables and hypotheses

Variable	Initial Value	Mean*	Volatility (Standard Deviation)**
Interest Rate	5%	10%	10%
Economic Growth	1%	3%	10%
TSX Biotech Index Growth	2%	3%	10%
Risk Premium	135 basis point (b.p.)	200 b.p.	20%
VC, IPO, Alliances and M&A	817.3	30%	25%
Federal Funding	481	10%	5%
Private Funding Other Than VC	956.6	-	-
Random Shock	0.5	0%	10%

* The mean is the long-term value of the variable

** Volatility captures the change of the value around its mean over each simulation.

One thousand simulations are performed using the initial values of the key variables and the hypotheses stated in Table 5.5 in order to estimate the supply of capital to the Canadian biotechnology sector over the next five-year period. Several sensitivity analyses are also performed based on varying the initial set of variables presented in Table 5.5.

5.2.5 SUPPLY SIMULATION RESULTS

Only three of the thousand scenarios obtained with the selected initial set of variables and hypotheses are used in the paired capital supply and demand scenarios that are presented in the following section. These are the minimum scenario, the mean scenario and the maximum scenario. Since the supply estimates come from a simulation process, only their resulting paired capital demand and supply scenarios are presented and analyzed in the next section. The respective supply estimates are presented in Table 5.6. The therapeutics share of capital supply is grossly estimated to be 80%. This percentage is in line with the observed percentage of capital allocated to the therapeutics segment that was reported earlier for the interviewed sample of stakeholders.

Table 5.6 Canadian cumulative and average supply estimates over the period 2001-2006 (Biotechnology sector and therapeutics sub-segment, billions of CAN$)

	Supply estimate scenarios		
	Minimum scenario	**Mean scenario**	**Maximum scenario**
Cumulative (2001-2006)	10.6	18.7	42
Average annual	2.12	3.73	8.3
Cumulative to therapeutics (80%)	8.5	14.93	33.3
Average annual to therapeutics (80%)	1.7	3	6.7

CHAPTER 6

PAIRED SCENARIOS OF CAPITAL SUPPLY AND DEMAND

6.1 SCENARIO CONSTRUCTION AND PRESENTATION

The second objective of this study is to evaluate the adequacy of capital supply and demand for Canadian companies in the therapeutics sub-segment. Results from the first two steps that are necessary to evaluate capital adequacy were presented in sections 4 and 5, respectively. They are estimates of the capital required to bring molecules currently being developed and to be developed in the product development pipelines of Canadian firms, and estimates of the amount of capital potentially available from the various supply sources. In this section, we present two paired scenarios of capital supply and demand based on the estimates obtained in the previous sections. These paired scenarios allow us to draw conclusions about the volume of external capital that must come from the capital markets in the U.S. and elsewhere in order to satisfy any potential shortfall obtainable in Canada. Finally, an analysis of any mismatch between capital supply and demand completes this section.

Three important considerations in terms of input vectors need to be addressed in order to make balanced and well-thought judgment calls about the existence of a potentially significant mismatch between capital supply and demand. They are:

- Choice of appropriate cost and attrition rate vectors;
- Choice of the initial state and growth of the Canadian molecules pipeline, more specifically, those molecules that are or will be actively developed by the Canadian firms over the forecasting period; and
- Inherent volatility of supply determinants and the resulting stochastic shocks that influence their behaviour.

Several scenarios about potential capital requirements were presented in section 4. In the following section, only two estimated demand scenarios are used. Each scenario corresponds to the two alternative pipelines of Canadian molecules to be considered as being actively developed in the coming years. They are the Industry Canada 2001 study full pipeline, and the sample of Canadian molecules reported in the Recombinant Capital 2001 database. These capital demand estimates (see the third and the fourth scenarios presented in Tables 4.3 and 4.6) are then used to build two different sets of paired scenarios of capital demand and supply. In the first set of paired scenarios, McKinsey cost and attrition rate vectors are used (Scenario 4, tables 4.3 and 4.6). This scenario is used because it is based on costs and attrition rates reflecting the expected improvements in R&D productivity, and the scenario uses an annual growth rate of 15% in the number of molecules entering the pre-clinical stage (Scenario 4, tables 4.3 and 4.6). The main justification for choosing a 15% growth rate is that it has been the observed historical growth in the number of compounds that entered the pre-clinical stage in Canada over the period 1999-2001. Results from the first pairing of capital demand and supply scenarios are presented in Table 6.1 and are analyzed below.

The second pairing of demand and supply scenarios are presented in Table 6.2. They differ from those reported in Table 6.1 since they use the less optimistic PricewaterhouseCoopers cost and attrition rate vectors (after improvements in R&D productivity) to estimate capital requirements (Scenario 3, tables 4.3 and 4.6). These significantly higher cost vectors lead to higher capital needs, and consequently to paired capital supply and demand scenarios where more capital has to come from external capital markets. The capital requirements estimates mentioned above also refer to what is considered to be the most probable growth rate of 15% in the number of molecules entering the pipeline over the next five years.

6.2 ANALYSIS OF THE MOST RELEVANT PAIRED CAPITAL DEMAND AND SUPPLY SCENARIOS

In the most probable scenario in Table 6.1, the average annual capital requirements corresponding to each of the previously mentioned pipelines are $3.5 billion and $1.2 billion, respectively (Scenario 4, tables 4.3 and 4.6). These average annual figures amount to aggregate capital requirements of $17.7 billion and $6.2 billion over a five-year forecasting horizon for each of the two pipelines considered. The corresponding average annual capital requirements (for the PricewaterhouseCoopers cost and attrition rate vectors after improvements in R&D productivity), which are reported in Tables 4.3 and 4.5 (third scenario), are $15.3 billion and $5.6 billion, respectively. These capital requirement estimates correspond to an **aggregate** capital requirement of $76.3 billion and $27.9 billion, respectively, over a five-year forecasting horizon.

The forecasting horizon over which the domestic supply of funds in the sector is forecast is limited to a five-year period because the variance of the estimate increases in direct proportion to the length of the time span that is being used. Longer forecasting periods imply wider confidence intervals for our estimates, and thus, may make these estimates less useful. The pipeline, which is reported in the Industry Canada study, refers to the total number of compounds being developed in Canadian therapeutics sub-segment companies. The pipeline drawn from the Recombinant Capital online database represents a subset of the Industry Canada pipeline; namely, that subset for which we assume Canadian firms or developers are publicly attempting to attract outside investors (particularly from the U.S.).

The initial state of capital supply in the Canadian economy, which was used in the simulation of capital supply performed in section 5, is based on estimates of the capital raised by Canadian biotech firms over the past three years (see Table 5.4).

A detailed analysis of the results for the two pairings of capital demand and supply scenarios completes this section. As a cautionary note, we repeat that judgement calls about the existence of a significant shortfall of capital supply to meet demand should be used prudently. Since many complex and dynamic factors are at play, any forecasted shortfall in the supply of funds should not necessarily be interpreted as symptomatic of the need for capital rationing by individual biotech firms. For example, we would expect that firms are not actively pursuing the development of all the molecules reported in the Industry Canada 2001 study. In practice, firms voluntarily prioritize the development of their most potentially successful targets. This results from deliberate strategic choices of firms, and is not due to capital rationing per se. In other words, decisions not to pursue the development of all molecules could occur even without any capital shortfall. For example, limited existing capabilities may constrain and limit the scope of development activities of the sector or of specific individual firms in that sector. Capital availability is only one of the many variables that influence the strategic choices of biotech firms. Moreover, capital rationing (or the so-called equity gap) exists only when molecules offering more than an adequate risk-adjusted return cannot be financed.

Table 6.1: First set of pairings of scenario estimates of Canadian supply and demand of funds over the period 2001-2006 (Therapeutics sub-segment, billions of CAN$)

	Supply estimate scenarios					
	Minimum scenario		Mean scenario		Maximum scenario	
Average annual	2.12		3.73		8.3	
80% Average annual to therapeutics	1.7		3		6.7	
	Demand estimate scenarios (therapeutics sub-segment)[12]					
	Industry Canada Pipeline	Recombinant capital sample	Industry Canada Pipeline	Recombinant capital sample	Industry Canada Pipeline	Recombinant capital sample
Average	3.5	1.2	3.5	1.2	3.5	1.2
	External financing estimates for the paired scenarios					
	Minimum scenario		Mean scenario		Maximum scenario	
Average	1.8	(0.5)	0.5	(1.8)	(3.2)	(5.5)

Table 6.2: Second set of parings of scenario estimates of the Canadian supply and demand of funds over the period 2001-2006 (Therapeutics sub-segment, billions of CAN$)

	Supply estimate scenarios					
	Minimum scenario		Mean scenario		Maximum scenario	
Average	2.12		3.73		8.3	
80% Average annual to therapeutics	1.7		3		6.7	
	Demand estimate scenarios (therapeutics sub-segment)[13]					
	Industry Canada Pipeline	Recombinant capital sample	Industry Canada Pipeline	Recombinant capital sample	Industry Canada Pipeline	Recombinant capital sample
Average	15.3	5.6	15.3	5.6	15.3	5.6
	External financing estimate paired scenarios					
	Minimum scenario		Mean scenario		Maximum scenario	
Average	13.6	3.9	12.3	2.6	8.6	(1.4)

[12] Based on the McKinsey cost and attrition rate vectors after improvements in R&D productivity, scenario 4 in tables 4.3 and 4.6.

[13] Based on McKinsey costs and attrition rates vectors before improvements in R&D productivity, scenario 3 in tables 4.3 and 4.6.

Based on the results reported in Table 6.1 for the capital requirements obtained using the most probable 15% growth rate in the number of molecules, only the minimum supply scenario suggests a substantial need for external financing. This is based on the hypothesis that 80% of the total $2.12 billion in biotech financing is used for the more capital-intensive therapeutics sub-segment. The average external financing estimate for this minimum scenario is substantial at $1.8 billion over an average $3.5 billion capital requirement or demand estimate. For all other scenarios, there is no indication of any possible capital shortfall. For example, the mean supply estimate of $3 billion and the corresponding $0.5 billion in external financing requirements do not appear to be out of range with what could be reasonably be expected to be raised from external capital markets. All other scenarios, which are associated with the McKinsey cost and attrition rate vectors after improvements in R&D productivity and the 15% growth rate in the number of molecules, indicate that Canadian supply matches estimated capital requirements, even for the probably overstated number of molecules under development in the total development pipeline.

Thus, it seems appropriate to expect that no real capital shortfall will exist if the productivity gains and corresponding lower costs associated with the McKinsey study are realized. Nevertheless, one should be careful about our interpretation of the results for this first set of paired capital demand and supply scenarios. First, serious doubts have been raised about the ability of the industry to reduce costs and failure rates and to capture potential productivity gains, at least over the short term. As was emphasized in section 4, recent data tend to demonstrate that not only have cost reductions not yet been observed but that development time is still increasing. Second, while no significant capital shortfall exists overall, this does not necessarily mean that supply is appropriate at all stages of the financing continuum (i.e., from seed financing to public offerings of debt and equity). Finally, the availability of sufficient capital does not mean that all valuable molecules will be financed on competitive terms. The matching exercise tells

us little about the competitive structure of capital supply, or about the bargaining power of the demanders of capital. In other words, micro-economic factors in the various market niches that may not be highly integrated do matter.

The results for the sets of paired capital demand and supply scenarios reported in Table 6.2 suggest a fairly different conclusion. When the more pessimistic PricewaterouseCoopers cost and attrition rate vectors are used, substantial external financing is needed for most sets of paired capital demand and supply scenarios, especially for those that use the total pipeline of molecules in development (Industry Canada pipiline 2001). Even for the supply mean scenario of $3 billion, an overwhelming annual average of $12.3 billion in external financing is needed. A substantial amount of external financing is even needed to fund the much smaller number of products under development captured by the Recombinant Capital sample. Whether the results for the Recombinant capital mean paired capital demand and supply scenario imply that there would exist a significant capital shortfall is debatable. However, obtaining $2.6 billion of the total $5.6 billion total capital requirements through external financing would probably be difficult, since Canadian and U.S. macroeconomics factors that affect capital supply are quite highly correlated. Thus, based on the results for the paired capital demand and supply scenarios reported in Table 6.2, a significant capital shortfall would exist unless a very substantial fraction of the molecules reported in the total pipeline do not have real economic value and thus, will not be developed in practice.

6.3 EVALUATION OF THE ADEQUACY OF CAPITAL SUPPLY AND DEMAND

The interested reader should consider two additional issues before arriving at a final judgment about the existence of a significant capital shortfall based on the results presented in Tables 6.1 and 6.2 for various paired capital demand and supply scenarios. These two issues are:

First, are Canadian cost and attrition rate vectors the same as the U.S. vectors used herein, and which of the two input vectors used in the preceding capital requirements estimations are the most appropriate proxies for their Canadian counterparts given the Canadian pipelines of molecules used in our study?

Second, what fraction of the total pipeline of molecules reported in the Industry Canada study is being actively developed or has real economic value from a risk-adjusted return perspective?

The following comments provide some guidance on the two above considerations. Most of the interviewed experts agree that the number of molecules being actively developed (and willingly selected as economically more relevant) is significantly lower than the total number of molecules that are reported as being under development. It is known in the industry that no new investment is occurring for many of the reported molecules, and this lack of investment does not appear to be based on internal capital rationing. Since firms are clearly signalling their search for external capital when they list their molecules in the Recombinant Capital database, one can hypothesize that this sample of Canadian molecules is a lower bound with respect to the number of economically relevant molecules. In section 4, we stress that the Canadian molecules reported in the Recombinant Capital database account for about one third (33%) of the capital requirements associated with the total Canadian pipeline. Thus, the $2.6 billion in external financing reported in Table 6.2, which relates to the mean paired capital demand and supply scenario (PricewaterhouseCoopers input vectors after improvements in R&D productivity), is potentially a meaningful lower bound. If the McKinsey input cost and attrition rate vectors (after improvements in R&D productivity) are the appropriate inputs, then no external capital is needed.

Most specialists in the field consider the PricewaterhouseCoopers cost vectors to be overstated, at least for the actual state of the Canadian pipeline, and given that Canadian costs are lower than their American counterparts. Recent presentations in bio-conferences indicate that development costs do not conform to the McKinsey input values, but instead continue to rise with the increase in average development time. Hence, the evidence suggests that the more optimistic cost structure is unlikely to prevail in Canada in the near future. As a consequence, a potential and significant capital shortfall is possible at least over the next five years. What is even more certain is that Canadian firms may be very vulnerable to the need to raise substantial funds in external capital markets, even if only a limited number of the total pipeline of reported molecules are developed actively.

CHAPTER 7

CONCLUDING REMARKS

The intent underlying this research was to characterize the supply of capital for Canadian biotechnology firms. This is made following two objectives. The first objective is to identify the issues and difficulties of financing biotechnology in Canada from the viewpoint of supply stakeholders, and the second objective is to assess the capacity of Canadian suppliers of capital to meet the predicted demand of Canadian biotech firms.

Analysis of the viewpoint of interviewees on the various dimensions that are relevant to biotechnology financing led to the following conclusions:

- While the quality of science in Canada is world-class and has a high credibility, not many Canadian firms have a dominant position in terms of size and pipeline development.
- The lack of management is one of the major problems in Canada not only in terms of a limited number of good managers, but also in terms of the extent and variety of experience and skills. Hiring a CEO abroad is often a necessity in spite of the difficulties and costs involved.
- The lack of management does seriously affect the financing process of a biotech firm because it is one of the major reasons for not providing funding by investors. As supply siders mentioned, business models and concepts originating from Canada are models that have appeared earlier in the U.S.
- Attracting U.S. investors is not easy for an average size Canadian firm. U.S. stakeholders need a strong local co-investor, but they know few such local investors with a good track record of investing in successful companies.

- Investors generally agree that there is often total misunderstanding of finance by Canadian promoters and that the Canadian financing environment is too institutional and too protected.
- The development of the private risk capital industry in Canada is then of great necessity and importance. Indirect sources of capital, such as pension funds, are also to be encouraged to be more involved with the bio-industries.
- Also, more competition in the Canadian venture capital industry would be beneficial. In fact, not only do relatively few pools of capital operate at the venture level but the competition between these groups appears to be relatively low.
- The second major problem with Canadian biotech financing is that firms go public very prematurely. Canadian institutions should be educated to better support biotech companies earlier in the process so that they can replace the IPO financing round with a mezzanine round so that they have enough financial resources for the next stage of development. They could then postpone the timing of their IPO until their market cap and valuations are such that they can float an issue whose secondary trading has liquidity.
- The lack of market liquidity in Canada is a major problem in biotech financing for even solid and profitable firms. Having programs or fiscal measures that encourage investment in the biotech sector at the retail level as well as help to develop broader knowledge would certainly be helpful.

Access to appropriate term financing is a critical factor for being in a competitive position and exploiting all of the future growth opportunities for the Canadian biotech firms. We evaluate the equivalence of the supply and demand of capital for the Canadian therapeutics sub-segment by estimating the amount of capital required by the sector over a mid-term planning horizon (five years, a period long enough to develop

appropriate financing policies at firm and government levels) by determining the capital potentially available for investment in the Canadian biotechnology industry to finally draw a picture of the adequacy of demand and supply.

- Considering the full pipeline of molecules of Canadian firms belonging to the therapeutics sub-segment (Industry Canada study 2001) and the development costs and attrition rate vectors after improvements in R&D productivity (see tables A.2 and A.3 in Appendix A for details about the development phases), aggregate demand estimates range from $16.9 billion and $18.5 billion depending on the growth rate of the number of molecules entering the pre-clinical testing stage each year over 5 years. This corresponds to an annual capital need ranging from $3.4 billion and $3.7 billion if the growth rates considered are 10% and 20% respectively.
- The base case we considered to analyze the adequacy of supply and demand of funding assumes a growth rate of new molecules entry of 15%. The need of capital corresponding to this growth rate is of $17.7 billion over five years, an average annual amount of $3.5 billion.
- The capital demand for each stage of development corresponding to the above-mentioned estimates are:

  Pre-clinical: $7.1 billion
  Phase I: $3.9 billion
  Phase II: $2.4 billion
  Phase III: $4.2 billion
  Approval: $0.1 billion

- These annual capital requirements are greater than the amounts historically raised by the Canadian biotechnology sector and are quite sensitive to the development cost and attrition rate vectors considered.

- Estimates show that technological changes do not necessarily reduce capital requirements and that the latter are strongly and positively related to the stringency of the regulatory process. This suggests that regulatory policy may have an uneven impact on the development of the various biotechnology segments, and especially on the relatively more regulated therapeutics sub-segment.

- Simulations of the amount of capital potentially available to the biotech sector produced estimates ranging from $10.6 billion and $42 billion with a cumulative mean of $18.7 billion over the next five years. The therapeutics sub-segment share is grossly estimated to be 80%, thus, the supply of funds for this sub-segment is estimated to range from a minimum of $1.7 billion, a maximum of $6.7 billion, and an average of $3 billion annually.

- Using the most probable 15% growth rate in the number of molecules and McKinsey costs and attrition rates vectors after improvements in R&D productivity, only the minimum supply scenario suggests a substantial need for external financing of $1.8 billion for the therapeutics sub-segment. When the more pessimistic PricewaterouseCoopers cost and attrition rate vectors after improvements in R&D productivity are used, substantial external financing is needed for all the supply scenarios considered. Note that judgement calls about the existence of a significant shortfall of capital supply to meet demand should be used prudently. Since many complex and dynamic factors are at play, any forecasted shortfall in the supply of funds should not necessarily be interpreted as symptomatic of the need for capital rationing by individual biotech firms.

7.1 DEFICIENCIES IN OUR KNOWLEDGE ABOUT THE FINANCING OF CANADIAN BIOTECHNOLOGY COMPANIES

The interviews conducted in Canada and the United States capture the viewpoints of capital suppliers in terms of financing-related issues and difficulties. This study also presents a global assessment of the potential match between capital demand and supply over the next five years. An analysis of the interviews and the scenarios of capital supply and demand provide a better understanding of the structure, workings, and level of performance of the financing system and the financing networks used by both users and providers of biotechnology capital in Canada.

Many unknowns remain with regard to the possible policies and measures that could be implemented to address the various issues we documented. Specific policy issues include: i) whether or not effective public policies can be formulated to alleviate the most negative financing consequences resulting from the structural problems that characterize Canadian capital markets; ii) how Canadian firms are affected by the trend toward consolidation, and the types of actions that can be implemented to assist Canadian biotech stakeholders to develop deeper and more mature pipelines; iii) the level of growth in the development of new molecules that is expected from Canadian science during the next five years, iv) the interaction and effect of specific competency problems on the pace of development of Canadian firms, and v) how the natural evolution toward more mature firm pipelines combined with science-risk reduction resulting from appropriate financing to keep science in the universities longer and improvements in technology transfer and firm spin-offs, can significantly reduce financing-related difficulties. In turn, this may make venture capital financing and later-stage financing in Canada more comparable with the risk/return trade off faced by a typical U.S. firm.

Except for the most extreme mismatch scenarios of capital demand and supply (for example, one where capital requirements correspond to the PricewaterhouseCooper

higher cost vector and the Canadian pipeline is the one from the 2001 Industry Canada survey), the total amount of capital needed to be raised from external capital markets appear to be attainable, if necessary measures are implemented to address the most problematic issues. Even if our most probable paired capital demand and supply scenarios do not lead towards large equity gaps at the macro level, this does not necessarily imply that serious capital rationing will not exist for some firms or at some stages of the product development process. Major financing difficulties that need to be addressed include the limited liquidity of the Canadian capital market, the lack of substantial private mezzanine rounds of financing, premature IPO activity by Canadian biotech firms, and problems with specific competencies and size. These problems will significantly affect the ability of the Canadian biotechnology sector to create value.

Thus, while this study significantly contributes to a lessening of our knowledge deficiency in biotech financing in a Canadian context, substantial further work remains. Avenues for further study include:

A study of the role and impact of public financings on product development in the biotech industry, and on whether or not such financings should be targeted at the early or later stages of the biotech product development process;

A study to determine if there is an optimal firm size for biotech firms, and the role of public policy, alliances, mergers and acquisitions in facilitating the achievement of an optimal firm size if it exists;

A study to identify the determinants of the life cycles of individual product developments, product development pipelines, biotech firms and the biotech industry, and on how these life cycles evolve and interact over time; and

A study of the IPOs (initial public offerings) and SOs (seasoned offerings) of biotech firms to assess the short-term and longer-term performance of such offerings, including after-market liquidity, risk-adjusted returns, value creation, analyst following and subsequent offerings.

APPENDIX A

INPUT VARIABLES AND THEIR QUANTIFICATION

A.1 Number of molecules

The average duration for each development stage is measured in months. The distribution of the numbers of molecules over the total duration of a given stage accounts for the attrition rate for that stage.[14] The 306 molecules reported in Table A.1 as being in the 2001 pipeline for the Canadian therapeutics sub-segment represent 171 public and private Canadian companies (Industry Canada et al., 2001). The Canadian 1999 pipeline contained 224 molecules (Investment Partnerships Canada et al., 1999). Although the coverage differs for these two pipelines,[15] the annual growth in the total number of molecules tested is 15% over this two-year period.

Table A.1. Distribution of the molecules in the pipelines for the therapeutics sub-segment

Development stage	Number of molecules in the pipeline			
	For firms (January 1999)	For firms (April 2001)	Growth 1999-2001 (%)	For Recap firms (November 2001)
Pre-clinical	92	133	45	35
Phase I	63	62	-2	35
Phase II	38	69	82	32
Phase III	31	35	13	25
Approval	NA	7	NA	5
Total	224	306	37	132

Sources: Investment Partnerships Canada et al. (1999), Industry Canada et al. (2001), Recombinant Capital (2001), and Ernst & Young (2001), respectively.

The distribution of molecules by development stage drawn from the Recombinant Capital online database (website: www.recap.com) also is presented in Table A.1. This is a subset of the Canadian pipeline where the molecule developers are publicly attempting to attract the attention of outside investors. This sub-sample is used as a

[14] To illustrate, assume 100 molecules exist in the pre-clinical stage at time 0, that the duration of this stage is 2 months, and that the attrition rate of molecules that fail to pass this stage is 50%. The monthly attrition rate is 25% if attrition rates are, by assumption, distributed uniformly over time. If z is the number of molecules that entered the pipeline in each of the two previous months, z equals 57.14 in z*(1-50%/2) + z = 100. Thus, 100 molecules in pre-clinical trials at time 0 represent 57.14 and 42.85 molecules in their first and second month trials, respectively.

[15] The 1999 Canadian survey includes 65 firms.

proxy for estimating the external capital requirements for the 2001 pipeline for the Canadian therapeutics sub-segment.

A.2 Growth rates in the number of molecules

The scenarios with new molecule entry are designed to measure the effect of no and positive growth in the number of new approved drugs over the next five-year horizon. This effect is captured by increasing the number of molecules entering the pipeline at each point in time when the vectors of attrition rates are assumed to be constant over time.[16]

The base case annual growth rate is proxied by the past growth of 15% in the Canadian pipeline (see Table A.1). To test the sensitivity of the capital requirement estimates to this choice of input value, growth rates of 10%, 20% and 30% also are used. While a 30% annual growth rate appears unrealistic during the next five years, this is the annual rate proposed in the literature (e.g., PricewaterhouseCoopers, 1998, p. 2). If a pharmaceutical company wants to maintain its historical growth rates in R&D expenses and productivity, it has to launch four to six times more drugs than it currently does over the following seven years. This corresponds to average annual growth rate of 20% to 30%.[17] The 0% and 10% annual growth rates are used to capture pessimistic estimates of the expected growth in pipeline molecules.

A.3 Development durations

The average development durations are drawn from Bhandari et al (1999, p. 63). They are 8.5 years for development, consisting of 18-month periods for each of the pre-clinical, phase I, phase II and approval stages, and 30 months for the phase III stage. Although these average durations are similar to those reported by Spilker (1998) and McIntyre (2000), the sensitivity of the capital requirement estimates to a six-month increase in the average durations also is examined.[18]

A.4 Molecule development cost and attrition rate vectors

The molecule development costs and attrition rates used herein are presented in Tables A.2 and A.3. Only the values in Table A.2 reflect the expected improvements in R&D productivity of the two sources of this data. The drug development cost data reported in these two tables are expressed in terms of cost per approved drug and cost per compound tested in a certain stage. The first measure is useful for assessing the total cost of bringing a new drug to market, whereas the second measure facilitates a

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[16] This monthly rate is derived from the annual growth rate g by applying the formula $\sqrt[12]{1+g}-1$.

[17] Precisely, the average annual growth rates are $\sqrt[7]{4}-1=21.9\%$ and $\sqrt[7]{6}-1=29.2\%$, respectively.

[18] These new development durations do not exceed the maximum values reported in the literature.

computation of the total cost per stage. This latter cost measure is simply obtained by multiplying the number of molecules being tested in a given development stage by the stage cost per tested compound. Since the duration of the development stage always exceeds a month, we assume that costs are distributed uniformly across time.[19]

Table A.2 Typical development cost and attrition rate vectors in the biopharmaceutical industry before improvements in R&D productivity

Development Stage	Stage failure rate (%)	Stage cost per:		
		Approved drug (Millions of US$)	Approved drug (% of total costs)	Tested compound (Millions of US$))
Panel A: Scenario 1[a]				
Pre-clinical	50	66	13.2	6.6
Phase I	30	67	13.4	13.5
Phase II	55	167	33.4	47.9
Phase III	15	150	30.0	95.6
Approval	25	50	10.0	37.5
Total	90[b]	500	100	NA
Panel B: Scenario 2[a]				
Pre-clinical	50	59	25.9	5.9
Phase I	30	37	16.0%	7.3
Phase II	57	66	29.1	18.9
Phase III	33	65	28.5	43.3
Approval	0	1	0.4	1.0
Total	90[b]	228	100	NA

[a]Scenarios 1 and 2 use the development cost and attrition rate vectors before improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively.

[b]This reports the cumulative attrition rate over the entire development process.

[19] A simple example helps to understand this assumption. Assume that the cost at the pre-clinical stage per compound tested is equal to $ 6 million. If 100 compounds enter the pre-clinical stage during a certain time period, then the total pre-clinical stage cost for these 100 compounds is $ 600 million. The cost is distributed equally across the number of months in the pre-clinical stage.

Table A.3 Typical development cost and attrition rate vectors in the biopharmaceutical industry after improvements in R&D productivity

Development Stage	Stage failure rate (%)	Stage cost per:		
		Approved drug (Millions of US$)	Tested compound (Millions of US$))	% change in stage cost per tested compound due to R&D productivity improvements
Panel A: Scenario 3[a]				
Pre-clinical	75	140	22.1	+235[b]
Phase I	10	50	31.5	+133
Phase II	30	75	52.5	+10
Phase III	0	60	60.0	-37
Approval	0	45	45.0	+20
Total	84[c]	370	NA	NA
Panel B: Scenario 4[a]				
Pre-clinical	50	59	5.9	0
Phase I	44	38	7.7	+5
Phase II	57	23	8.3	-56
Phase III	17	36	29.8	-31
Approval	0	1	1.0	0
Total	90[c]	157	NA	NA

[a]Scenarios 3 and 4 use the development cost and attrition rate vectors after improvements in R&D productivity obtained from PricewaterhouseCoopers (1998) and McKinsey (Bhandari et al., 1999), respectively.
[b]This value is equal to 100 * [(22.1 from Table A.2 – 6.6 from Table A.1) / 6.6 from Table A.1].
[c]This value is the cumulative attrition rate over the entire development process.

The attrition rates presented in these two tables represent the percentage of compounds that fail to go to the next stage of the development process. In order to switch from costs per approved drug to costs per compound tested, we need to compute cumulative attrition rates, or the percentage of compounds that fail eventually to go to market.[20] As is the case for costs, the assumption is that total attrition is distributed uniformly across development time for each development stage.[21]

[20] If r_x represents the attrition rate of stage x and n is the total number of development stages in the model, then:

cumulative attrition rate *for* stage, or $x = 1 - \prod_{i=x}^{n}(1 - r_i),\ x = 1,...,n$

[21] More precisely, we assume that the *number* of molecules failing to pass a certain stage is distributed uniformly across time, and not the *attrition rate* per se.

The development cost and attrition rate data are obtained from sources that draw very different conclusions about total drug development costs, and the impact of the technological revolution induced by genomics and bio-informatics on the development cost and attrition rate vectors through their favourable impact on R&D productivity. These differences are due to major methodological differences between the two data sources. The PricewaterhouseCoopers methodology concentrates on changes in the product development mix across development stages. Advances in drug discovery technology can lead to an increase in the number of molecules tested in early R&D stages, and thereby increase attrition rates and costs at these early stages. Furthermore, eliminating molecules at earlier stages means reduced failure rates in clinical stages, where costs are relatively high. Their combined effect leads to an overall decrease of 26% in the total cost per approved drug. In contrast, the McKinsey methodology focuses only on the effects of the genetic revolution on the clinical development process. Pharmacogenomics, defined as "the ability to tailor drugs to the genetic makeup of individual patients", can reduce costs in advanced clinical phases in three ways (Bhandari et al., 1999, p. 58). First, pharmacogenomics helps to detect toxicity problems earlier and therefore reduces the number of compounds to be tested in phases II and III. Second, this technology enables a better pre-selection of patients elected for trials, which leads to a decrease in the number of patients in late clinical trials. Finally, pharmacogenomics can also reduce the length of trials.[22] Taken together, genetic diagnostics can lead to a reduction of more than 30% in total costs per approved drug after accounting for the additional phase I costs related to this technological change.

Although the two sources explain R&D productivity gains in very different ways, they both forecast a significant decrease in the total cost incurred to bring a drug up to the market due to expected gains in R&D productivity. Nevertheless, the total cost estimates by PricewaterhouseCoopers are over 100% higher than those by McKinsey both before and after expected improvements in R&D productivity are reflected in the development cost and attrition rate vectors.[23]

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[22] We do not directly incorporate this last effect into the duration vector, in order to keep our analysis comparable across different data sources. For more details about the effects of genetic diagnostic on clinical drug development, see Bhandari et al. (1999), pp. 62-65.

[23] These substantial differences are not unique to the data sources used herein. To illustrate, a U.S.$ 194 million figure (in 1990 dollars) is reported by the U.S. Congress, Office of Technology Assessment (p. 72), and a value of about U.S.$ 500 million is reported by the Pharmaceutical Research and Manufacturers of America.

APPENDIX B

DESCRIPTION AND COMPARATIVE ANALYSIS OF THE FINANCIAL DATA OF CANADIAN AND U.S. PUBLIC FIRMS

We conducted a comparative analysis of various measures of financial condition and performance for samples of Canadian and U.S. biotech firms over the five-year period, 1996-2000. The initial results for six measures of financial condition and performance are reported in panels A through F of Table B.1. These measures are total assets, annual sales, annual R&D expenses, gross margin (%), return on assets (%) and return on common equity (%). In the remainder of this section, we concentrate on the mean and median values for the various measures of financial condition and performance. The mean provides the average value of each measure for each sample of firms, and the median provides the value of each measure for a typical firm in each sample.[24]

Based on the results for the entire time period reported in panel A of Table B.1, the mean and median total assets, annual sales, R&D expenses and gross margins are significantly lower for the Canadian biotech firms. The mean and median returns on total assets and on common equity are negative for both samples of firms, and not significantly different for the Canadian compared to the U.S. biotech firms. While the mean and median total assets, annual sales, R&D expenses and gross margins are lower for the Canadian biotech firms, only the differences in their mean values are both lower and consistently significant for the Canadian biotech firms on a year-by-year basis.

To make the comparison more meaningful, we adjust for the smaller average size of the biotech firms in the Canadian sample by restating the measures of financial condition and performance on first a per dollar of assets basis, and then a per share basis. The results on a per dollar of assets basis for the entire period and each of the five years from 1996 to 2000 are reported in panels A through F, respectively, of Table B.2.

Over the entire time period, the mean and median sales per dollar of assets are significantly smaller for the Canadian biotech firms, and the median R&D expenses (book value) per dollar of assets are significantly larger (smaller) for the Canadian biotech firms. These results are fairly robust on a year-by-year basis. The major exception is the differences in the medians for R&D expenses per dollar of assets that have the correct sign but are not always significant on a year-by-year basis.

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[24] The median also is used because the distribution of values for each measure of financial performance and condition is not always normal.

The results on a per share basis for the entire period and each of the five years from 1996 to 2000 are reported in panels A through F, respectively, of Table B.3. Over the entire time period, the mean and median per share total assets and per-share sales are significantly lower for the Canadian biotech firms. While both the mean and median per share book values and per share R&D expenses are lower for the Canadian firms, only the differences in their respective medians are statistically significant. While both the mean and median earnings per share from operations and cash flows from operations are less negative for the Canadian biotech firms, only the differences in their respective medians are statistically significant. These results are not robust given the considerable variation in the significance of the differences in the means and medians on a year-by-year basis.

We now use regression techniques to examine the possible relationship between various measures of financial condition and performance stated on a per-share basis and the stage of development of the product pipelines of the firms. Since we have the state of the pipelines for 1998 and 2000, we run a series of pooled time-series and cross-sectional regressions for the Canadian sample of biotech firms. These results are summarized in Table B.3. Based on these results, variations in per share total assets, per share sales, cost of goods sold, liquidity per share, book value per share, earnings per share, return on assets and return on equity are significantly related to the stage of development of product pipelines. With the exception of cost of goods sold, the estimated coefficients that are significant are usually those for the number of molecules in the later stages of the product development pipeline. Interestingly, variations in R&D expenses are not significantly related to the development of the number of molecules in each stage of the product development pipeline.

Table B.1 Basic measures of financial condition and performance for Canadian and U.S. biotech firms, 1996-2000

Panel A: 1996-2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	131	99.80	30.89	226.14	0.71	1279.20	2234	1148.96	40.35	4735.64	0.04	44069.30	10.27	0.00	0.02
Annual sales	155	48.96	2.72	169.75	0.00	1191.70	2284	884.64	12.80	3834.62	0.00	40363.20	10.27	0.00	0.00
Annual research and development expense	141	10.77	4.68	26.09	0.06	261.08	2223	92.46	8.28	376.37	-0.16	5029.71	9.87	0.00	0.00
Gross margin	155	8.21	0.00	35.26	-42.58	194.50	2283	478.96	0.46	2216.20	-186.71	26376.00	10.13	0.00	0.01
Return on assets	130	-0.37	-0.23	0.65	-4.89	0.40	2224	-0.44	-0.19	1.15	-20.76	0.84	-0.71	0.48	0.10
Return on common equity	130	-0.45	-0.26	1.18	-8.32	5.04	2221	-0.08	-0.14	8.59	-136.84	234.19	0.49	0.62	0.00

Panel B: 1996

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	25	87.62	31.23	196.12	7.68	865.93	425	1008.18	32.95	4124.76	0.11	32136.25	4.52	0.00	0.54
Annual sales	25	49.19	2.76	166.41	0.00	818.86	425	787.66	9.34	3477.95	0.00	35284.00	4.30	0.00	0.06
Annual research and development expense	23	6.11	3.22	7.21	0.61	32.19	416	71.14	6.62	274.75	0.00	2344.84	4.80	0.00	0.14
Gross margin	25	4.80	-1.32	25.80	-12.62	116.18	425	404.11	0.00	1845.35	-65.14	15880.00	4.45	0.00	0.09
Return on assets	25	-0.11	-0.12	0.22	-0.48	0.40	422	-0.36	-0.16	0.91	-9.20	0.42	-1.38	0.17	0.53
Return on common equity	25	-0.12	-0.13	0.30	-0.76	0.63	422	-0.34	-0.13	2.13	-24.43	15.73	-0.52	0.60	0.83

Panel C: 1997

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	28	86.80	31.52	202.00	4.06	915.15	435	1030.52	39.61	4193.36	0.07	37494.17	4.61	0.00	0.25
Annual sales	28	50.72	3.16	179.89	0.00	929.98	436	827.33	12.04	3545.26	0.00	35764.00	4.49	0.00	0.01
Annual research and development expense	26	7.55	4.25	8.38	0.84	37.39	427	86.80	7.63	368.17	0.00	5029.71	1.10	0.27	0.02
Gross margin	28	7.22	0.00	33.10	-20.93	144.42	436	431.98	0.28	1936.18	-62.94	16741.00	4.57	0.00	0.12
Return on assets	28	-0.29	-0.28	0.31	-0.81	0.38	434	-0.43	-0.19	1.38	-20.76	0.77	-0.54	0.59	0.05
Return on common equity	28	-0.39	-0.30	0.56	-2.63	0.47	434	-0.14	-0.17	3.30	-11.76	51.47	0.40	0.69	0.02

Panel D: 1998

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	36	79.71	24.71	197.19	0.73	1048.70	476	1072.77	34.16	4469.60	0.22	40685.50	4.79	0.00	0.30
Annual sales	36	44.19	2.79	168.96	0.00	1001.50	478	822.33	12.17	3647.11	0.00	37154.00	4.60	0.00	0.00
Annual research and development expense	33	8.98	5.61	9.91	1.36	49.12	466	90.82	8.64	352.77	0.00	2860.60	4.98	0.00	0.11
Gross margin	36	7.68	0.00	35.17	-28.43	158.90	478	442.94	0.11	2069.85	-79.51	17688.00	4.59	0.00	0.49
Return on assets	35	-0.46	-0.27	0.68	-3.13	0.25	474	-0.57	-0.25	1.29	-15.60	0.67	-0.50	0.62	0.61
Return on common equity	35	-0.48	-0.36	1.42	-4.64	5.04	474	0.06	-0.18	12.70	-88.83	234.19	0.25	0.80	0.06

Panel E: 1999

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	33	123.25	27.07	261.12	0.71	1279.20	470	1234.12	40.41	5130.56	0.04	44069.30	4.61	0.00	0.37
Annual sales	36	55.92	2.05	202.49	0.00	1191.70	477	928.87	14.02	3948.56	0.00	38125.00	4.75	0.00	0.01
Annual research and development expense	33	14.68	7.33	27.18	0.74	138.82	462	97.57	9.28	407.55	0.00	4036.00	4.24	0.00	0.21
Gross margin	36	9.57	0.00	44.07	-42.58	194.50	477	527.16	0.90	2396.98	-162.47	23023.00	4.71	0.00	0.17
Return on assets	33	-0.59	-0.28	0.99	-4.89	0.27	468	-0.48	-0.24	1.15	-18.27	0.84	0.51	0.61	0.87
Return on common equity	33	-0.79	-0.29	1.69	-8.32	2.25	468	-0.30	-0.13	10.13	-136.84	127.24	0.28	0.78	0.05

Panel F: 2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Total assets	9	168.47	41.29	353.05	29.14	1107.27	428	1400.35	71.22	5591.53	0.25	42917.00	0.66	0.51	0.32
Annual sales	30	44.47	2.78	126.20	0.00	640.00	468	1044.67	18.31	4435.45	0.00	40363.20	4.85	0.00	0.01
Annual research and development expense	26	15.42	4.25	50.46	0.06	261.08	452	113.91	9.80	448.77	-0.16	4436.00	1.12	0.26	0.01
Gross margin	30	10.98	0.02	34.27	-27.20	134.58	467	578.55	2.39	2679.35	-186.71	26376.00	4.57	0.00	0.26
Return on assets	9	-0.20	-0.16	0.23	-0.73	0.08	426	-0.35	-0.15	0.91	-14.28	0.79	-0.49	0.62	0.74
Return on common equity	9	-0.28	-0.22	0.27	-0.86	0.11	423	0.30	-0.12	8.82	-16.41	158.41	0.20	0.84	0.09

Table B.2 Basic measures of financial condition and performance on a per dollar of total assets basis for Canadian and U.S. biotech firms, 1996-2000

Panel A: 1996-2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	131	0.75	0.83	0.22	-0.24	0.99	2231	0.43	0.70	2.89	-127.07	1.00	-1.26	0.21	0.00
Sales per dollar of assets	134	0.27	0.09	0.38	0.00	2.47	2236	0.50	0.38	0.50	0.00	6.46	6.55	0.00	0.00
Cash flow from operations per dollar of assets	122	-0.34	-0.21	0.64	-4.72	0.30	1920	-0.34	-0.17	0.87	-14.56	0.94	-0.04	0.97	0.35
R&D per dollar of assets	121	0.37	0.23	0.56	0.02	5.42	2172	1.28	0.62	7.64	-0.01	325.86	1.31	0.19	0.00

Panel B: 1996

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	25	0.82	0.90	0.18	0.33	0.97	425	0.50	0.76	1.52	-26.90	0.99	-1.03	0.31	0.02
Sales per dollar of assets	25	0.30	0.09	0.38	0.00	1.22	424	0.51	0.33	0.59	0.00	6.15	1.76	0.08	0.07
Cash flow from operations per dollar of assets	24	-0.13	-0.14	0.22	-0.54	0.30	375	-0.30	-0.16	0.73	-6.61	0.41	-1.10	0.27	0.66
R&D per dollar of assets	23	0.28	0.20	0.24	0.04	0.81	413	0.89	0.58	1.00	0.00	7.17	8.68	0.00	0.00

Panel C: 1997

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	28	0.81	0.87	0.17	0.29	0.98	435	0.30	0.75	6.15	-127.07	0.99	-0.44	0.66	0.01
Sales per dollar of assets	28	0.26	0.07	0.33	0.00	1.02	435	0.48	0.34	0.44	0.00	2.53	3.34	0.00	0.05
Cash flow from operations per dollar of assets	26	-0.25	-0.27	0.29	-0.79	0.30	371	-0.32	-0.17	0.96	-11.28	0.71	-0.39	0.70	0.23
R&D per dollar of assets	26	0.30	0.24	0.25	0.02	0.92	425	1.75	0.65	15.81	0.00	325.86	0.47	0.64	0.00

Panel D: 1998

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	36	0.71	0.76	0.23	-0.15	0.97	476	0.45	0.66	0.76	-5.59	0.99	-5.07	0.00	0.08
Sales per dollar of assets	36	0.28	0.09	0.34	0.00	1.13	477	0.49	0.39	0.44	0.00	3.41	2.80	0.01	0.02
Cash flow from operations per dollar of assets	33	-0.45	-0.28	0.69	-3.00	0.27	406	-0.49	-0.26	1.21	-14.56	0.68	-0.17	0.87	0.60
R&D per dollar of assets	32	0.36	0.29	0.31	0.02	1.23	462	1.39	0.68	3.65	0.00	63.56	1.59	0.11	0.00

Panel E: 1999

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	33	0.70	0.73	0.26	-0.24	0.99	425	0.52	0.71	0.70	-5.96	1.00	-1.41	0.16	0.05
Sales per dollar of assets	33	0.33	0.15	0.50	0.00	2.47	429	0.49	0.34	0.55	0.00	6.46	2.32	0.02	0.01
Cash flow from operations per dollar of assets	31	-0.51	-0.21	0.95	-4.72	0.28	361	-0.26	-0.10	0.61	-5.44	0.60	1.31	0.19	0.58
R&D per dollar of assets	30	0.50	0.26	0.97	0.03	5.42	454	1.44	0.64	5.29	0.00	104.23	0.97	0.33	0.00

Panel F: 2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Book value per dollar of assets	9	0.71	0.77	0.24	0.21	0.97	425	0.52	0.71	0.70	-5.96	1.00	-0.78	0.44	0.31
Sales per dollar of assets	12	0.10	0.03	0.15	0.00	0.46	429	0.49	0.34	0.55	0.00	6.46	7.84	0.00	0.00
Cash flow from operations per dollar of assets	8	-0.16	-0.16	0.25	-0.66	0.12	361	-0.26	-0.10	0.61	-5.44	0.60	-0.46	0.64	0.48
R&D per dollar of assets	10	0.43	0.17	0.61	0.05	2.03	418	0.90	0.52	1.78	-0.01	33.00	0.84	0.40	0.20

Table B.3 Basic measures of financial condition and performance on a per-share basis for Canadian and U.S. biotech firms, 1996-2000

Panel A: 1996-2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	130	2.76	1.31	4.77	0.04	31.69	2223	8.02	3.55	22.23	0.01	630.97	8.33	0.00	0.00
Book value per share	130	1.85	0.94	2.66	-0.04	16.98	2220	3.72	2.28	18.91	-637.66	492.17	1.13	0.26	0.00
Sales per share	134	1.14	0.11	3.77	0.00	29.97	2235	4.53	0.99	10.34	0.00	135.55	8.65	0.00	0.00
Earnings per share from operations	131	-0.20	-0.19	0.64	-2.59	1.87	2228	-0.77	-0.36	9.58	-385.10	7.71	-0.68	0.50	0.00
Cash flow from operations per share	122	-0.05	-0.17	0.82	-2.12	4.25	1915	-0.43	-0.34	9.09	-328.20	17.49	-0.46	0.65	0.00
R&D per share	121	0.37	0.23	0.56	0.02	5.42	2172	1.28	0.62	7.64	-0.01	325.86	1.31	0.19	0.00

Panel B: 1996

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	25	3.42	1.82	6.28	0.25	31.69	421	6.94	3.49	12.44	0.01	124.81	1.41	0.16	0.01
Book value per share	25	2.45	1.46	3.30	0.13	16.03	421	3.75	2.54	5.52	-19.50	60.90	1.17	0.24	0.02
Sales per share	25	1.73	0.17	5.96	0.00	29.97	422	4.68	0.87	11.61	0.00	114.06	1.26	0.21	0.01
Earnings per share from operations	25	-0.07	-0.12	0.57	-0.89	1.87	421	-0.23	-0.33	1.45	-8.04	7.71	-1.14	0.26	0.12
Cash flow from operations per share	24	0.01	-0.15	0.99	-0.94	4.25	373	0.03	-0.29	2.11	-7.62	17.49	0.09	0.93	0.20
R&D per share	23	0.28	0.20	0.24	0.04	0.81	413	0.89	0.58	1.00	0.00	7.17	8.68	0.00	0.00

Panel C: 1997

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	28	2.18	1.26	3.13	0.11	16.23	434	8.72	3.74	32.44	0.03	630.97	1.07	0.29	0.00
Book value per share	28	1.67	0.95	1.87	0.05	8.77	434	2.44	2.56	31.28	-637.66	56.49	0.13	0.90	0.00
Sales per share	28	0.98	0.11	3.12	0.00	16.49	435	4.84	0.96	11.26	0.00	107.16	4.83	0.00	0.00
Earnings per share from operations	28	-0.18	-0.24	0.55	-1.38	1.38	434	-1.19	-0.36	18.54	-385.10	7.58	-0.29	0.77	0.20
Cash flow from operations per share	26	-0.07	-0.19	0.68	-0.97	2.56	370	-0.86	-0.35	17.20	-328.20	16.83	-0.23	0.82	0.04
R&D per share	26	0.30	0.24	0.25	0.02	0.92	425	1.75	0.65	15.81	0.00	325.86	0.47	0.64	0.00

Panel D: 1998

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	35	2.15	0.96	3.38	0.05	18.55	474	8.00	3.29	18.09	0.01	277.46	5.80	0.00	0.00
Book value per share	35	1.43	0.78	1.88	-0.02	9.57	474	3.83	2.01	13.28	-41.16	246.26	1.07	0.29	0.00
Sales per share	36	0.96	0.09	3.00	0.00	17.72	476	4.28	0.97	9.12	0.00	82.51	5.09	0.00	0.00
Earnings per share from operations	35	-0.19	-0.16	0.66	-1.86	1.70	474	-0.90	-0.42	5.08	-93.07	5.76	-0.82	0.42	0.02
Cash flow from operations per share	32	-0.10	-0.16	0.80	-1.58	2.81	404	-0.64	-0.42	5.79	-96.67	15.56	-0.52	0.60	0.03
R&D per share	32	0.36	0.29	0.31	0.02	1.23	462	1.39	0.68	3.65	0.00	63.56	1.59	0.11	0.00

Panel E: 1999

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	33	3.38	1.01	6.18	0.04	24.78	468	9.03	3.46	28.45	0.01	533.37	1.14	0.26	0.00
Book value per share	33	2.06	0.77	3.54	-0.04	16.98	468	4.43	1.83	23.64	-35.40	492.17	0.58	0.57	0.05
Sales per share	33	1.28	0.10	3.68	0.00	20.41	469	4.58	1.16	9.66	0.00	87.33	4.22	0.00	0.00
Earnings per share from operations	33	-0.28	-0.22	0.73	-2.59	1.47	468	-1.22	-0.41	9.42	-171.85	6.34	-0.57	0.57	0.05
Cash flow from operations per share	31	0.02	-0.17	0.86	-0.98	3.33	405	-0.66	-0.35	8.98	-170.02	15.33	-0.42	0.67	0.04
R&D per share	30	0.50	0.26	0.97	0.03	5.42	454	1.44	0.64	5.29	0.00	104.23	0.97	0.33	0.00

Panel F: 2000

	Canada						U.S.						Tests for difference		
	N Valid	Mean	Median	Std. Dev	Min	Max	N Valid	Mean	Median	Std. Dev	Min	Max	t	t-Sig. (2-tailed)	Median test sig
Assets per share	9	2.87	1.60	3.03	0.70	8.60	426	7.28	4.16	10.15	0.03	78.57	1.30	0.19	0.09
Book value per share	9	1.57	0.96	1.47	0.59	5.26	423	4.10	2.59	5.30	-7.77	58.97	1.43	0.15	0.02
Sales per share	12	0.39	0.03	0.69	0.00	2.27	433	4.28	0.99	10.07	0.00	135.55	1.34	0.18	0.02
Earnings per share from operations	10	-0.37	-0.17	0.76	-2.42	0.25	431	-0.25	-0.31	1.21	-4.37	6.39	0.32	0.75	0.19
Cash flow from operations per share	9	-0.25	-0.17	0.84	-2.12	1.05	363	0.02	-0.27	1.64	-4.07	9.01	0.48	0.63	0.31
R&D per share	10	0.43	0.17	0.61	0.05	2.03	418	0.90	0.52	1.78	-0.01	33.00	0.84	0.40	0.20

Table B.4 Pooled time-series and cross-sectional regression results for basic measures of financial condition and performance on a per-share basis against the number of molecules in each stage of the product pipeline for Canadian biotech firms for 1998 and 2000

Dependent variable	Notes			Independent variables							
				Constant	Research	Pre-clinical	Phase I	Phase II	Phase III	Approval	Launched
Assets per share	n	41	b_i	1.49	-0.03	-0.27	0.05	0.01	-0.27	1.10	1.20
	r^2	0.58	t	4.43	-0.22	-1.83	0.27	0.08	-1.02	4.81	2.91
	sig	0.00	Sig	0.00	0.82	0.08	0.79	0.94	0.32	0.00	0.01
Book value per share	n	42	b_i	0.87	-0.01	-0.15	0.12	0.09	0.02	0.41	0.93
	r^2	0.45	t	3.51	-0.12	-1.34	0.86	0.69	0.12	2.37	3.03
	sig	0.003	Sig	0.00	0.90	0.19	0.40	0.50	0.91	0.02	0.01
Earnings per share	n	65	b_i	-0.19	0.02	0.03	-0.03	-0.05	0.00	0.29	-0.10
	r^2	0.21	t	-1.77	0.45	0.51	-0.52	-0.82	0.01	3.32	-0.98
	sig	0.047	Sig	0.08	0.66	0.61	0.60	0.42	0.99	0.00	0.33
Return on assets (%)	n	41	b_i	-0.35	-0.01	-0.07	0.06	-0.18	0.20	0.17	0.18
	r^2	0.34	t	-3.12	-0.15	-1.51	0.99	-2.94	2.27	1.79	1.39
	sig	0.04	Sig	0.00	0.88	0.14	0.33	0.01	0.03	0.08	0.17
Return on equity (%)	n	41	b_i	-0.35	-0.05	-0.13	0.07	-0.21	0.17	0.10	0.17
	r^2	0.29	t	-2.09	-0.69	-1.70	0.77	-2.18	1.24	0.85	0.81
	sig	0.10	Sig	0.04	0.49	0.10	0.45	0.04	0.22	0.40	0.42
Sales per share	n	46	b_i	0.53	-0.01	-0.10	-0.11	0.01	-0.15	0.62	0.02
	r^2	0.53	t	3.61	-0.09	-1.51	-1.27	0.09	-1.18	5.84	0.09
	sig	0.00	Sig	0.00	0.93	0.14	0.21	0.93	0.25	0.00	0.93
Liquidity per share	n	43	b_i	0.74	-0.09	-0.10	0.12	-0.02	-0.12	0.26	0.94
	r^2	0.34	t	3.28	-0.91	-1.00	0.96	-0.13	-0.65	1.63	3.26
	sig	0.03	Sig	0.00	0.37	0.33	0.35	0.90	0.52	0.11	0.00
R&D per share	n	40	b_i	0.35	0.05	-0.05	0.06	0.01	-0.08	0.01	0.00
	r^2	0.17	t	4.25	1.58	-1.66	1.47	0.19	-1.31	0.20	0.05
	sig	0.52	Sig	0.00	0.12	0.11	0.15	0.85	0.20	0.85	0.96
Cost of goods sold	n	44	b_i	0.50	0.09	-0.09	0.04	0.02	-0.19	0.23	-0.09
	r^2	0.33	t	4.52	1.76	-1.88	0.73	0.39	-2.07	2.93	-0.65
	sig	0.03	Sig	0.00	0.09	0.07	0.47	0.70	0.05	0.01	0.52

APPENDIX C

INTERVIEW GUIDE

UQÀM **Chair in Management of Bio-Industries**
School of Management Sciences
University of Quebec in Montreal

Adequacy of Demand and Supply for Capital
in the Canadian Bio-Industries
Characterization of Supply

Interview-Guide

Please note that:

1. The questionnaire is sponsored by the Chair in Management of Bio-Industries (University of Quebec in Montreal) on behalf of Industry Canada and Statistics Canada.

2. The purpose of this questionnaire is to characterize the supply of capital for Canadian biotechnology firms.

3. Any information collected by this questionnaire will be treated in a confidential manner.

4. Your participation is voluntary.

Thank you for your cooperation.

Part I: General Organization Information

Name of the organization: _____

Name of the interviewee: _____

Location: ☐ Canada ☐ United States ☐ Public ☐ Private

Type of stakeholders:

- ☐ Venture Capitalist
- ☐ Bank/Investment Banker (IPO and Stock Issues Specialists)
- ☐ Alliance/Acquisition Specialist
- ☐ Capital Market Specialist
- ☐ Institutional Investor And Para-Public Entity
- ☐ Canadian Government Officer (Grants, fiscal and tax credits…)
- ☐ Labour-Sponsored Group
- ☐ Other (Specify): _____

Financial information as of December 31, 2000:

- Total capital under management: _____
- Source of the funds and Amount:
  - o Public pension funds _____
  - o Private pension funds _____
  - o Corporations _____
  - o Insurance companies _____
  - o Individual investors _____
  - o Foreign investors _____
  - o Government _____
  - o Other _____
- Investment policy
  - o Percentage in venture capital: _____
  - o Percentage invested in biotech firms: _____
- Total number of investee biotech companies in the portfolio: _____
  - o Number of Canadian investee companies in the portfolio: _____
- Total cost of the investee portfolio ($million): _____
  - o Cost with Canadian investee portfolio ($million): _____

Target segment*:

☐ Biopharmaceutical & Biomedical	☐ AgroAl Biotech	☐ Bioenvironmental
☐ Therapeutics / Pharmaceuticals	☐ Plant	☐ Water
☐ Diagnostics	☐ Applied Biotechnology	☐ Soils & Sites
☐ Biotechology	☐ Bio-Process	☐ By-products
☐ Genomics	☐ Genomics	☐ Air
☐ Combinatorial Chemistry	☐ Industrial Bio-Process	☐ Diagnostic Equipment
☐ Proteomics	☐ Bio-product	☐ Other:
☐ Gene therapy	☐ Veterinary	
☐ Bio-Medical / Bio-equipment	☐ Animal	
☐ Drug Delivery	☐ Applied Biotechnology	
☐ Clinical Research	☐ Bio-product	
☐ Medical Device	☐ Veterinary	
☐ Other:	☐ Other:	

☐ Other		
☐ Bio-informatics	☐ Chemicals	☐ Resources
☐ Forest Products	☐ Nutraceuticals / Cosmeceuticals	☐ Energy & Mining
☐ Other:		

* See below for a detailed list of activities and for the Glossary

Target biotech companies:

☐ Start-ups, early-stage companies (R&D and prototype development; Pre-clinical phase & Phase I)

☐ Late-stage companies (companies having made significant progress clinically; Phase II & III)

☐ Later expansion companies, Nearing market launch (The approval phase and/or in the commercialization stage)

☐ Publicly traded companies

☐ Other (Specify): _____

Initial and Follow-on Investments in Canadian biotechs as of December 31, 2000

Investee company	Investee information	Stage	Total deal size	$ Invested	Type of financing	Co-Investors	$Invested by Co-Investors
Name: City: Prov.:	☐ New ☐ Follow-on ☐ Other	☐ If other specify:			☐ If other specify:		
Name: City: Prov.:	☐ New ☐ Follow-on ☐ Other	☐ If other specify:			☐ If other specify:		
Name: City: Prov.:	☐ New ☐ Follow-on ☐ Other	☐ If other specify:			☐ If other specify:		

- How many deals are you involved with as a leader? _____
- How much will you invest in biotechnology within each of the next two years? _____
- How much in Canadian biotech firms? _____
- What is your cut-off desired rate of return? _____

Part II: Information about financing issues and difficulties when investing in the Canadian biotechnology sector

Dimensions
Issues and difficulties will be handled according to the stage of development and the following dimensions:

1. **Type of project to finance**
   - Quality science and technology
   - Management team: whether they have had any commercial hits before or not.
   - Intellectual property: according to the number and the quality of the patents the firm may have.
   - Scientific due diligence procedures
   - Major reasons why they do not provide funding for a project/stage?
2. **Different perceptions of risk and return**
   - Unpredictability of the biotech sector
   - Gestation time: time to get products (or drugs) on the market
   - Failure to deliver products to the clinic
   - Failure to reach the critical mass necessary for public funding
   - Did you ever ask for special warrant deals or equity at bargain-basement prices before investing in Canadian biotech firms?
   - What are your goals of return on investment?
3. **Difficulty in valuing biotech firms**
   - Evaluation methods of various groups of suppliers: How do they determine value?
   - How do their practices differ from other competitors (domestically and/or internationally)?
   - When funding in stages, what are the timing and the amount of each portion?
4. **Level of owner commitment and financial participation in the project**
5. **Disclosure of information**

6. **Strategic alliances / Mergers & Acquisitions**
   - Big brothers: whether the biotech partners with a big (or international) pharmaceutical company or not.
   - Do you ask companies to pursue Mergers & Acquisitions as a requisite to future financing?
7. **Government commitment and/or guarantees for managing risk**
8. **Other relevant dimensions**

Financing issues and difficulties according to the stage
(Bio-Pharmaceutical / Bio-Medical)

Financing Issues and Difficulties / *Development Stage and Commercialization*	**DIMENSION**						
	Type of project to finance	**Different perceptions of risk and return**	**Difficulty in valuing biotech firms**	**Level of owner commitment and financial participation in the project**	**Disclosure of information**	**Strategic alliances / Mergers & Acquisitions**	**Government commitment and /or guarantees for managing risk**
Basic Research (Discovery Phase) **IMAGING**							
Applied R&D (Pre-clinical Phase) **INCUBATING**							

Product Development and Engineering (Clinical Phase) **DEMONSTRATING**	
FDA Review / Approval	
Production and marketing (Commercialization Phase) **PROMOTING & SUSTAINING**	

Detailed activities for the Bio-Pharmaceutical / Bio-Medical segment

- [ ] **Biomaterials / Tissue Engineering**
  - [ ] Transplants and implants
  - [ ] Bioprostheses
  - [ ] Other
- [ ] **Biomedical**
  - [ ] Biomechanics / Biophysics
  - [ ] Bio-equipment / Instrumentation
  - [ ] Medical imagining
  - [ ] Mode of administration and sustained release medications
  - [ ] Radiology
  - [ ] Other
- [ ] **Diagnostics**
  - [ ] Allergy
  - [ ] Cardiology / Angiology
  - [ ] Cytology
  - [ ] Dermatology
  - [ ] Gastroenterology
  - [ ] Genetics
  - [ ] Genitourinary / STDs
  - [ ] Gynecology / Infertility
  - [ ] Hematology / Biochemical analysis
  - [ ] Immunology
  - [ ] Infectiology
  - [ ] Metabolism / Hormones
  - [ ] Musculo-skeletal
  - [ ] Nephrology
  - [ ] Neurology
  - [ ] Oncology
  - [ ] Parasitology
  - [ ] Respiratory
  - [ ] AIDS
  - [ ] Urology
  - [ ] Virology
  - [ ] Other
- [ ] **Nutraceuticals / Cosmeceuticals**
- [ ] **Clinical Research**
  - [ ] Cardiology / Angiology
  - [ ] Dietetics / Applied nutrition
  - [ ] Endocrinology
  - [ ] Gastroenterology
  - [ ] Gentitourinary
  - [ ] Hematology
  - [ ] Hepatology
  - [ ] Immunology
  - [ ] Infectiology
  - [ ] Musculo-skeletal
  - [ ] Nephrology
  - [ ] Neurology
  - [ ] Oncology
  - [ ] Ophtalmology
  - [ ] ENT
  - [ ] Parasitology
  - [ ] Pathology
  - [ ] Pneumology
  - [ ] Rhumatology
  - [ ] AIDS
  - [ ] Virology
  - [ ] Other
- [ ] **Pharmaceuticals / Therapeutics**
  - [ ] Anesthetics
  - [ ] Antiinfectives
  - [ ] Cardiovascular / Atherosclerosis / Angiology
  - [ ] Dermatology
  - [ ] Gastroenterology
  - [ ] Genitourinary / STDs
  - [ ] Gynecology / Infertility
  - [ ] Hematology
  - [ ] Immunology
  - [ ] Metabolism / Hormones
  - [ ] Musculo-skeletal
  - [ ] Neurology / Central nervous system
  - [ ] Oncology

Detailed activities for the Bio-Agro-AI segment

- **Plant**
  - **Production**
    - Biotechnologies
    - Health animal
  - **Extraction / Manufacturing**
    - Bioproducts
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

- **Animal**
  - **Production**
    - Biotechnologies
    - Health animal
  - **Extraction / Manufacturing**
    - Bioproducts
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

Detailed activities for the Bio-Environment segment

- **Air**
  - **Biotechnologies**
    - Industrial bioprocesses
    - Environmental biotechnologies
    - Genetic engineering
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

- **Water**
  - **Biotechnologies**
    - Industrial bioprocesses
    - Environmental biotechnologies
    - Genetic engineering
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

- **Soil and sites**
  - **Biotechnologies**
    - Industrial bioprocesses
    - Environmental biotechnologies
    - Genetic engineering
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

- **By-products**
  - **Biotechnologies**
    - Industrial bioprocesses
    - Environmental biotechnologies
    - Genetic engineering
  - **Technical services and analysis**
    - Laboratory analysis / sampling
    - Analysis of risk / Toxicology / Safety
    - Bio-equipment
    - Suppliers / Distributors -Biotechnologies

INTERVIEW GUIDE (CONTINUED)

GLOSSARY

GLOSSARY	
Analysis Of Risk	A risk factor includes all variables statistically linked to a studied event. All these factors constitute risk factors. Their more or less marked expression is translated by a heterogeneous breakdown of a population's exposure to risk.
Anti-infectives	Drugs used to treat infectious diseases; includes antibiotics for bacterial diseases and antivirals for viral diseases.
Applied Biotechnologies	Application of genetic engineering principles to various sectors of exploitation; e.g., all techniques using parts of or living organisms to produce varieties that improve plants or animals (agri-food and resources) to develop micro-organisms to trap pollution
Aquaculture	Management and development of the potential of aquatic resources and environments for the commercial production of animal or plant species through mastery of their biological cycles.
Bio-informatics	Discipline encompassing all aspects of the acquisition of biological information; i.e. storage, treatment, distribution, analysis, and interpretation.
Bio-materials / Tissue Engineering	Use of natural (e.g. coral) or synthetic (non-organic such as Teflon) materials not rejected by the human body and without undesirable side effects to develop implants, prostheses, transplants, or to allow the controlled release of drugs and components.
Bio-mechanics	Modelisation study of musculo-skeletal system and the human body and movement analysis.

GLOSSARY	
Bio-medical	That which is directly related to medicine as well as biology. Here, we mean it in the context of biomedical engineering; i.e., art of building equipment useful in biology and medicine.
Bio-pharmaceutical	Any substance derived from a gene sequence or that is in some way related and having therapeutic properties.
Bio-products	Products manufactured with living cells (plant, bacteria, or animal) or their components using biotechnological processes.
Bio-technologies	Use of living organisms to develop new products. Can use whole organisms (yeast and bacteria) or natural substances (enzymes) derived from organisms. Described as processes and genetic engineering
Cellular Culture	Everything referring to harvesting the cells of a living organism and growing them in the lab. Animal cell culture differs from that of microorganisms or bacteria by the media used, incubation and cellular passage parameters.
Clinical Research	Clinical research is a medical activity concerning humans that aims to improve knowledge of a disease or treatment. In pharmacology, clinical research is characterized by studies of the medication given to humans in the context of clinical studies.
Cloning	Asexually producing genetically identical copies of genome of a living organism. Includes both molecular cloning (isolating DNA sequence of interest and obtaining multiple copies of it in an organism) and cellular cloning.
Diagnostics	Development of tools in order to help doctors evaluate a patient's medical history, the symptoms and data of a physical examination and other tests to associate them with an identified disease.
DNA Probe	Molecule, usually a nucleic acid marked with a

GLOSSARY	
	radioactive isotope, colouring agent, or enzyme. Used to find the sequence of a specific gene or nucleotide.
Extraction / Manufacturing	Transfer of the constituents of the solid or liquid phase into another phase or product.
Forestry Products	Includes wood products (woodworking products, windows, doors, kitchen cupboards, floor coverings and mouldings) and pulp and paper products (packaging, diapers, glossy paper, tissue, and fine paper).
Gene Therapy	Method consisting of introducing genetic material (genes) into an organism's cells to correct pathological anomaly (mutation, alteration...). Often includes introducing a normally functioning gene into the cell where the existing gene has been altered.
Genetic Engineering	Overall set of techniques to isolate, sample, characterize, and transfer genes from one organism to another, i.e. modifying the genetic baggage of a cell via genetic manipulation.

INTERVIEW-GUIDE (CONTINUED)

DEVELOPMENT STAGES FOR THE BIO-AGRO-AL AND THE BIO-ENVIRONMENT SEGMENTS

Browsing	To develop and check the theory or the proven scientific knowledge in order to examine in the laboratory whether the solution is ready; to make complementary studies concerning the technical-economic aspects, engineering, the state of the market and to take measurements of the parameters connected to the micro-conditions of operation.
Experimentation	To ensure unfolding, on an average scale, conditions of operation by respecting qualitative and temporal standards (to establish the proof of the concept, development of prototype, to ensure intellectual protection, to specify the competing advantages, to determine the strategy of commercial valorization).
Demonstrating	To show technological reliability under standard conditions of operation.
Pre-Commercialization	To offer technology to industrial users (commercial profitability is not yet shown or is not proven); to determine the commercial interest although technology cannot be economically valuable (technology is in conformity with the industrial standards in the plan of reliability and the performance).
Commercialization	To show that technology is marketable and that it can be financially profitable.

APPENDIX D

LIST OF SUPPLIERS INTERVIEWED

NAME	COMPANY	POSITION
Aaron Schwimmer	Goldman, Sachs & Co.	Financial Analyst - Global Investment Research
Alexander W. Moot	Seaflower ventures	General Partner
Andrea Solari	Sanderling	Chief Financial Officer and Partner
Bernard Coupal	T2C2 – Transfer Technologies Commercialization Capital	President
Brenda Irwin	BDC Venture Capital	Director
Bruce Jackson	Pacific Horizon	General Partner
Cameron L. Groome	National Bank Financial	Investment Banking Biotechnology & Healthcare
Chris Ehrlich	Interwest Partners	Senior Associate
Chris Laird	Ventures West	Research Associate
Claude Camiré	Dundee Securities Corporation	Biotech Analyst
Claude Vezeau	BioCapital	Associate, Vice-president Investments
Cosme Ordonez	DLOUHYmerchant	Investment Analyst, Drugs & Vaccines
Dana R. Ono	Venture Investment Management Company LLC	Director
Darrell Elliott	MDS Capital Corp.	Senior Vice President
David J. Collier	CMEA Ventures	General Partner
David Shotland	CIBC World Markets	Managing Director Healthcare Investment Banking
David Witzke	Credit Suisse First Boston	Biotech Analyst
Douglas Miehm	RBC Dominion Securities	Managing Director, Global Equity Division, Biotechnology/ Pharmaceutical Research
Florence Rozen	MedTech Partners	Investment Analyst
Franklin Berger	J.P. Morgan Securities Inc.	Managing director
Geneviève Poulin	National Bank Financial	Analyst – Biotechnology & Healthcare
Gérald André	SGF Santé inc.	Vice President

NAME	COMPANY	POSITION
Gérard Gagné	Arthur Andersen & Cie	Manager
Graham K. Crooke	Asset Management Company	Venture Capital Partner
Hubert Carrier	SGF Soquia inc.	Vice President
Jack Weinstein	Ladenburg Thalmann	Managing director Investment banking
Jay B. Silverman	Silverman Capital Management LLC	General Partner
Jean Potvin	BDC – Business Development Bank of Canada	Investment Manager, Venture Capital
Jean-Christophe Renondin	MDS Capital	Senior Vice-President
Jean-Denis Dubois	Fonds de solidarité FTQ	Director, Investments Health and Biotechnology
Jean-Michel Petit	SOFINOV – Société Financière d'Innovation	Gestionnaire, Biotechnologies et sciences de la vie
Jit Patel	Astrazeneca	Director Discovery Alliances CNS
John J. Murphy	Agricapital Corporation	Senior Consultant for Canada
Joseph Regan	Ventures West	Vice President
Judy Blumstock	Royal Bank Capital Partners	Associate, Life Sciences Fund
Justin C. Stephenson	RBC Capital Partners Ltd.	Managing Partner, Life Sciences
Lori M. Robson	Bay City Capital	Chief Investment Officer
Louis A. Guilbault	SGF Soquia inc.	Scientific Director
Louis P. Lacasse	Gestion GeneChem inc.	President
Lynn Dymond	CMEA Ventures	Chief Financial Officer
Martin Godbout	Genome Canada	President & CEO
Michael Lytton	Oxford Bioscience Partners	General Partner
Mitchell Greenspoon	Yorkton Securities Inc.	Executive Vice-President
Monique Laliberté	KPMG Corporate Finance Inc.	Vice President
Patrice Vachon	Heenan Blaikie Lawyers	Lawyer
Peter C. M. McWilliams	Sanderling	Senior Associate
Pierre Cantin	CDP Sofinov	Associate, Biotechnology and Life Sciences
Rachel Leheny	Lehman Brothers	Senior Analyst - Biotechnology
René Douville	Royal Bank Ventures inc.	Vice President

NAME	COMPANY	POSITION
Richard Garant	Merck Frosst	Director, Corporate Affairs
Richard J. Dole	Quorum Funding Corporation	Partner
Richard L. Lockie	MDS Capital – Building Health and Life Science Companies	Senior Vice President
Robert Bechard	Royal Bank Capital Partners	Director, Life Sciences Fund
Robert C. Rech	Ferghana Partners INC.	Managing Director
Rodger E. Wyse	Burrill and Company	Managing Director
Roger L. Bernier	Foragen Technologies Mgt. Inc.	Vice-President Eastern Canada
Ross A. Jaffe	Versant Ventures	Managing Director
Sushant Kumar	Mehta Partners LLC	Partner
Tom Salemi	Asset Alternatives	Senior Editor Venture Capital & Health Care
Yad Garcha	Growth Works Capital Ltd.	Senior Vice President, Investment
Mike Kaplan	Three Arch Partners	General Partner

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