MEDICAL INNOVATION AND GOVERNMENT INTERVENTION

Reconciling Interests to Create Stakeholder Value

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"It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interest."

and

"People of the same trade seldom meet together, even for merriment and diversion, but the conversation ends in a conspiracy against the public, or in some contrivance to raise prices."

Adam Smith, "An Inquiry into the Nature and Causes of The Wealth of Nations" (1776), Modern Library, New York

Preface

Global health care issues are driving the public sector into a balancing act between conflicting and complementary forces of inevitable change: an ageing population, the explosion of new therapeutic technologies, a critical shortage of clinical professionals, the desire to improve clinical outcomes, and economic constraints.

With respect to technology and economic constraints, the public is in a confusing situation as it strives to lower current health care costs, but at the same time, seeks more and better health care technology. Moreover, in developing this new technology it is in the public's interest to foster successful new business development, increasing public wealth by creating jobs and the resulting tax revenues. Also, a healthier workforce is more productive, further enhancing the incentive for technology development.

Biotechnology has been seen as offering promises of breakthrough innovations and hence major business potential. These innovations are not incremental improvements but new and different types of therapy and diagnostics. Consequently, a number of governments have invested significant resources into creating a strong biotechnology industry base, with special emphasis on subsidizing drug development. Despite the success of some individual products, however, the infrastructure has so far not fully met expectations.

This book deals with the complex dynamics of the health care sector, assessing, in particular, the risks inherent with an enforced regulation of an entire industry sector. The major focus is on value creation in general and biotechnology in particular. Since drugs constitute the bulk of biotechnological health care applications, and likewise both drug development and pricing is under particular governmental regulation, the book highlights the pharmaceutical sector whenever possible. Both practitioners and policy makers will find the messages in this book helpful in creating value for their stakeholders.

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Professor Morton Kamien is Professor Emeritus of Economics and Decision Sciences. A distinguished scholar, Professor Kamien came to the Kellogg School over 35 years ago from Carnegie-Mellon University. At Kellogg, Kamien served as the School's associate dean for academic affairs for three terms, the Joseph and Carole Levy Distinguished Professor of Entrepreneurship and director of the school's Heizer Center for Entrepreneurial Studies. He retired in 2007.

Professor Kamien made fundamental advances in the use of game theory and dynamic optimization methods in industrial organization theory. Among his many publications are contributions that helped found the modern theory of limit pricing under uncertainty. Other work was instrumental in developing the theory of patent races – how firms compete to develop a new product or production method, the value of patents, mergers and entry deterrence. He has also produced two classic textbooks, co-authored with Kellogg peer Nancy L. Schwartz: *Dynamic Optimization: The Calculus of Variations and Optimal Control in Economics* (first published by North Holland in 1981) and *Market Structure and Innovation* (Cambridge University Press, 1982). For his contributions he was elected Fellow of the Econometric Society in 1996 and bestowed with an Honorary Doctor of Economics Degree in 2001 by Purdue University. At present he serves as an expert witness in anti-trust cases. Indeed, he was an expert witness on behalf of the plaintiff in the American Express vs. Visa and Master Card case which resulted in the largest anti-trust settlement in US history.

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Dr. Löffler served as advisor of: Baird Venture Partners; founding Board Member of the Biotechnology Institute, Washington DC; Biopharmaceutical Center at the WHU in Koblenz, Germany and multiple biotechnology companies. She consulted extensively on technology assessment issues for major pharmaceutical companies and Universities in the US. She also served at as the Board Member and Past-Chair, Council for Biotechnology Centers (BIO), and Board Member, Emerging Companies, Biotechnology Industry Organization and the Governor's Edgar Council for

Biotechnology. She was recently named one of the Tech 100 stars by *Crain's Chicago Business* and received the "Women in Black" I-Street award. She is completing her second book, *Rethinking the Biotechnology Model*. Dr. Löffler received her BS from the University of Minnesota, PhD from the University of Massachusetts and post-doctoral in biochemical engineering from Caltech.

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Professor Scott Stern is an Associate Professor of Management and Strategy at the Kellogg School of Management at Northwestern University. Stern is the co-organizer of the NBER Innovation Policy and the Economy Working Group and a Senior Fellow of the Searle Center on Law, Regulation and Economic Growth. He is an Associate Editor of *Management Science*, the *Journal of Industrial Economics*, the *International Journal of Industrial Organization*, serves on the Board of Management of the International Schumpeter Society, and has served on the editorial boards of the *Antitrust Law Journal* and the *Journal of Business and Economics Statistics*. In 2005, Stern was awarded the first Ewing Marion Kauffman Prize Medal for Distinguished Research in Entrepreneurship.

Stern explores how innovation – the production and distribution of "ideas" – differs from more traditional economic goods, and the implications of these differences for business and public policy. Often focusing on life sciences industries, this research is at the intersection between industrial organization and the economics of technical change. Recent studies examine the determinants of R&D productivity, the role of incentives and organizational design on the process of innovation, and the drivers of commercialization strategy for technology entrepreneurs.

Professor Stern graduated with a BA degree in Economics from New York University, and received his PhD in Economics from Stanford University in 1996. From 1995-2001, Stern was Assistant Professor of Management at the Sloan School at MIT, and, from 2001-2003, Stern was a Non-Resident Senior Fellow of the Brookings Institution.

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Kulvik has been involved in international multidisciplinary research projects, including those related to gene therapy and boron neutron capture therapy for brain tumors. His present topics include biotechnology management and strategy, as well as healthcare management and process analysis.

Martti Kulvik has consulted with several early-stage biotechnology companies, and he is a lecturer at the Institute of Medical Technology at University of Tampere and at the Department of Biological and Environmental Sciences at the University of Helsinki. Dr. Kulvik has authored and co-authored several medical journal articles as well as articles related to biotechnology management. He has also edited and co-authored two academic books.

Dr. Raine Hermans is the adjunct professor at the Helsinki School of Economics (forthcoming Aalto University). The Helsinki School of Economics (HSE) is the largest and leading business school in Finland and a globally acknowledged player in management education. At HSE, Dr. Hermans explores how the company or industry can create value by utilizing innovation management as a part of their everyday operations, strategic planning and valuation schemes.

Hermans was the visiting professor from 2006-2007 at the Kellogg School of Management, Northwestern University, Illinois, USA. At the Kellogg School of Management he performed studies on forecasting the future sales of the bio-pharmaceutical start-ups, analyzing biotechnologies as a competitive edge of the Forest industry, and simulating the impacts of biotechnology based energy applications together with experts from related fields. He visited Kellogg also in Summer of 2009 and led a research project on the projected economic impacts of the biopharmaceutical industry in Illinois. Before joining Kellogg he worked with ETLA – The Research Institute of the Finnish Economy, where he led multidisciplinary projects on managerial economics of biotechnology. He started with ETLA as a member of the forecasting group, responsible for international trade, and for production forecasts of the chemical, metal and electronics industries.

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Antti-Jussi Tahvanainen holds a research economist position at ETLA, the Research Institute of the Finnish Economy. He received his M.Sc. degree in economics and business administration from the Helsinki School of Economics in 2003, and is currently a Ph.D. student at the Helsinki University of Technology, Department of Industrial Engineering and Management. Tahvanainen was a visiting scholar at Stanford University in 2007 conducting research on university technology transfer offices and their value creation.

Tahvanainen has committed himself to understanding the role the development and commercialization of technologies play in the growth and prosperity of economies and single organizations. Through the analysis of impediments and key success factors in finance, organizational strategy, knowledge and technology management, technology transfer, and innovation policy, Tahvanainen aspires to contribute to the research of innovation and commercialization processes. He has published several articles in international journals and edited books.

Dr. Ismo Linnosmaa is a senior lecturer at the Department of Health Management and Policy, University of Kuopio. Dr. Linnosmaa received M.Sc. and Licentiate's degrees in economics from University of Joensuu and Ph.D. degree from the Department of Economics at State University of New York at Stony Brook, New York. Linnosmaa has worked as a research director at the Center for Pharmaceutical Policy and Economics, University of Kuopio, visiting lecturer at the Department of Economics, Boston University, and as a visiting research fellow at The Center for Health Economics, University of York. He also serves on the editorial board of *The Open Pharmacoeconomics & Health Economics Journal*.

Linnosmaa's research specializes in the fields of industrial organization and health economics. His research has focused on managerial incentives in oligopolistic firms and competition and incentives in the pharmaceutical industry. In recent years he has published several articles on price competition, regulation and advertising of pharmaceuticals. He has also contributed to evaluations of various pharmaceutical policy measures Finland has implemented in recent years.

Introduction by editors

Health care market conditions and regulation

Growing welfare systems have resulted in health care costs occupying a rising proportion of countries' GDP. Fifty years ago a relatively large proportion of workers' income was used for food and other basic necessities; since health care technology did not offer extensive diagnostic or treatment options, costs were not a major issue. As these technologies rapidly emerged, their costs have increased by at least an order of magnitude.

In addition to technological capabilities, the rise in health care consumption also reflects the changing values in virtually all Western societies: population surveys repeatedly indicate that health is the most valued component of welfare, ranking even higher than such highly prized wants as happiness, peace, and wealth. This demand is steady and strong in all Western countries and becomes more important as Third World countries continue to develop.

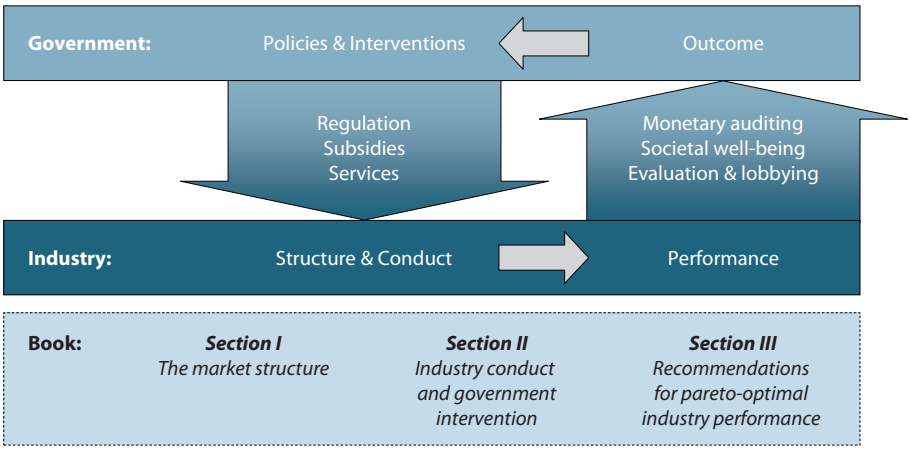
In a conventional market the customer's choices are strongly influenced by the perceived utility balanced by budget constraints. In the treatment of illnesses, however, a major distortion shapes the market: the payer is often someone other than the consumer of the service or product, for example, an insurance company or the government, and the individual no longer has a budget constraint. Consequently, the consumer benefits with increasing consumption [paid by someone else], and individual budget constraints and treatment prices no longer dominate consumer choice. Without regulation, health care customer preference should lead to a steady and significant raise in demand. This outcome holds true for any health care market where the majority of costs are paid by an insurance company or the public sector.

Further, while private health care providers have an incentive to increase profits, in almost all countries their fees are limited by government schedules. Even in the U.S., private insurers follow Medicare guidelines to determine their fees. Providers have, therefore, used volume and, especially, new technology to leverage increases in revenue.

The combination of provider-induced demand and public expectation for improved health care leads to strong pressure on expanding health care spending. This situation has led to extensive government interventions in virtually all health care systems, as the issue of affordability has become a key issue.

These interventions can be summarized in the following fashion (Figure 1):

Figure 1 Industrial organization and government interventions



The industry structure is influenced by such factors as the number of companies, the nature of the competitive environment, culture and judicial and political systems. The structure, in turn, will influence conduct, that is, how the players act individually and interact with each other – for example, do they innovate or imitate? Recoprocally, conduct can also influence the structure of the industry. For instance, companies can decide on vertical or horizontal integration strategies, which can reshape the industry structure. Moreover, conduct will directly influence performance as measured in monetary terms, or in other ways, like efficiency or quality of life. Based on performance, the industry will alter or maintain its structure and/or conduct.

If government desires to shape outcomes, it enacts policies (or laws) that change industry structure and/or conduct. For example, antitrust laws affect industry structure and policies that regulate prices limit industry pricing conduct. These effects can be far-reaching. Government pricing policies can for example cause a restructuring of the industry through such mechanisms as mergers, acquisitions or enhanced outsourcing. Government interventions can also enhance company profitability. Good examples are patents creating time-limited monopolies that provide incentives to invent.

Both government and industry agree that performance must be achieved in a pareto optimal fashion.[1] Nevertheless, friction may occur between the parties when deciding upon the distribution of the spoils of performance. For example, large profits are good for industry but the government may see them as excessive and harmful to public welfare. Government and industry may also disagree on what is the nature of the pareto optimal state. For example, government wants to maximize the health status of the entire population, while the industry desires to maximize profitability that may accrue from a smaller segment. These conflicts can cause further complications when government desires more than one optimal state, like lowering prices and fostering innovation. Lowering prices may help increase access to medications and improve population health status. In the long run, however, removing a profit motive may stifle innovation and worsen prospects for population health improvement.

Technology development under distinctive contexts

This book uses the above framework to assess the relation between health care market conditions, technology supply, and impacts of the government intervention. Broadly put, it analyzes the value creation mechanisms of technology development and commercialization from each of the health care stakeholder's perspectives. To offer an in-depth comparison, the focus here is on the impacts of biotechnology and drug development in the U.S. and Finland, countries with radically different health care system structures and very different environments for technology suppliers.

A government wants to accentuate the benefits of technology but eliminate the disadvantages through its interventions on structure and conduct. However, the government's dilemma lies in the inherent trade-off between two opposite effects. On one hand, it attempts to provide incentives for developing and adopting new technologies in order to create prosperous and profitable businesses by, for instance, allowing patent protection and thus creating monopoly power. On the other hand, it strives to distribute benefits to customers by boosting competition through generic introductions, cutting monopoly profits.

The development of biotechnologies has led to intensive patenting activity and, as a consequence, investment interest in innovative biotechnology companies.

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[1] In the simplest Pareto optimum or efficient state, any changes will result in one person being better off while another is worse off.

However, this intensity of proprietary technology has also become a clear obstacle for the development of new ventures. If a venture requires the licensing of dozens of previous patents, further development is discouraged as the early stage sunk costs become too high for a sound business. An individual IPR can form a gridlock in the value chain of developing a new technology (Heller and Eisenberg, 1998; Heller 2008). The IPR owner can exploit the entire value of a venture despite his or her property being a crucial but small sub-section of the value chain (Vanneste et al., 2006). This can lead to underuse of innovations and thereby forgone opportunities.

One way out of the gridlock is to pool intellectual property rights. There is a need for such pooling especially in biotechnology, where technologies are interdependent but tied to several independent patents. Governmentally controlled property right pools are one way to offer an increased total value for both society and business.

STRUCTURE OF THE BOOK

This book aims to shed light on the controversial issues discussed above. We use a framework that draws on the relationships in the above figure. Throughout we include discussions of governmental intervention in the forms of regulations and policies. Particular emphasis is on the effects of government efforts and tools to control the impacts of technology development on health care markets.

Section I The market structure

In any health care system, the large number of stakeholders generates a great degree of complexity. **Chapter 1** "Blueprint for Understanding Complex Health Care Systems" presents some initial definitions and two working models that will help the reader understand how and why different countries structure their health care systems the way they do, deal with and prioritize relevant stakeholders, and understand the effects of their strategic decisions on other elements of the health care marketplace. This chapter compares different health care systems, drawing on different features of these countries, for example, economics, politics, culture and population characteristics. This approach is taken because technology, and particularly the pharmaceutical industry, has experienced extensive cross-national integration, resulting in fewer but larger global giants.

Findings presented in **Chapter 2** indicate that health care technology-related applications are developed all over the world, and that they have received vast subsidies. This chapter utilizes biotechnology patent analysis as a measure for specialization and agglomerations. It suggests that while the origins of the value chains are globally dispersed large-scale actors at the downstream end of the chain (which require extremely high R&D and marketing expenditures) are spatially agglomerated across and within countries.

Section II Industry conduct and government intervention: policies and results

Chapter 3 assesses the juxtaposition between the government and the global pharmaceutical companies in the U.S., the world's largest pharmaceutical market. As is the case elsewhere, the American government's policy is Janus-faced: it tries to stimulate innovative activity of new drug development, but at the same time it exercises significant power aiming at reducing costs. This chapter, and the one that

follows, deal with the delicate balancing act between the pharmaceutical companies, on one hand, and the government, on the other. Chapter 3 discusses three acts meant to stimulate innovation and foster competition, each of which has had unforeseen consequences that can frustrate these good intentions. It also suggests a patent pooling system as a means of preventing a single patent owner, monopolizing a specific part of the value chain, to form a gridlock for any further innovation by setting the out-licensing price too high.

Chapter 4 provides information about how different price-regulation environments affect the price-cost margins of the pharmaceutical industry; or conversely, how pharmaceutical companies adapt to highly varying and changing regulatory environments. The U.S. pharmaceutical industries' price markups, or price-cost margins, are estimated against Finland's highly regulated governmental price-setting system. The results show that differences in regulatory environments have not historically altered the price markups in the pharmaceutical industry in these two countries. This finding indicates that in all but completely regulated markets the drug companies are able to adopt a market-specific pricing strategy that yields similar overall markups. From a governmental perspective, the results imply difficulty in setting up and sustaining an efficient price regulation system.

The previous chapters address the obvious trade-off between government subsidy programs for innovative health care technology and the expressed need for regulating rising health care costs. In the following two chapters, the aim is to add further perspective to the issue by drawing on the experience in one nation's quest to create a prosperous new industry: Finland's biopharmaceutical business.

Chapter 5 uses a simulation to analyze the future earnings of drug development projects of the Finnish bio-pharmaceutical small and middle-sized enterprises (SMEs), emphasizing the overall economic impacts and government and private venture financing requirements. The results of the simulation suggest that, because of rapidly growing R&D costs, high failure potential, and distant future earnings, early-stage drug development does not seem to be profitable. This finding implies a need for government intervention to facilitate or sponsor early-stage R&D efforts to bring along seed technologies for later stage technology development and trials. Developing funding and business affiliations with pharmaceutical giants has proven to be another way biotech companies can approach a balance between risks and return on a more sustainable basis.

While Chapter 5 explains why a government might want to support startup projects that present a negative net present value, **Chapter 6** elaborates on the consequences of governmental interventions/support in early and late phase drug development. It assesses how the use of the infant industry argument (IIA) could affect entrepreneurial strategies via injections of government financing. First how

the IIA-based subsidies and financing extend a conventional financial pecking order is shown in theory. Then the Finnish biopharmaceutical industry is empirically investigated. The results reveal the framework to be a relevant tool reflecting IIA-based policies in two primary ways: (1) Government subsidies are the most highly preferred financial instrument, favored even over companies' internal financing and (2) Government equity financing as a last resort and a relevant option only for companies with clearly non-market-oriented technology push strategies. The findings indicate that late stage support tends to cultivate loosers instead of market-oriented, vital companies, contrary to the original intentions of any government policy.

Section III Recommendations for optimal industry performance

In Chapter 7 the prior analyses are expanded by scrutinizing the impact of yet another much-debated government-initiated measure – the U.S. Bayh Dole Act, passed in 1980. This law promotes the diffusion of knowledge created in academic research by facilitating university-industry technology transfers. Specifically, the focus is on the role that American university technology transfer offices (TTOs), play in connecting and matching the substance of academic research with the need-driven demand of commercial markets.

The previous chapters have dealt with companies' responses to contradictory government intentions within the health care market. **Chapter 8** aligns the interests of the technology developers and other stakeholders in health care. These aligned interests are expressed in a model that creates a link among technology pricing, efficiency of treatment, and long-term health care costs. These aspects are contrasted with patient utilities received from acute and long-term care. The model serves as a tool for a health care planner, as well as a pricing starting point for a health care provider, with transparency being the embedded denominator.

Chapter 9 aims at realigning overall innovation policies and corporate strategies. Drawing on recent economic analyses, interviews with 89 business leaders, and seminar discussions within academia, government, and industry, a "bio-information based pharmaceutical" cluster is identified. It utilizes Finland's unique and voluntarily donated comprehensive patient data base and tissue banks as tools for creating domestic intellectual property pools. Such pools are attractive to the international pharmaceutical industry as part of their global value chain. By guarding the original data and material sources and opening cooperation and trade of extracted knowledge thereof, the government can not only act in line with the original interests of the donators to support domestic public health but even push it to a new level of international competitiveness.

We believe that this book's research and recommendations can be successfully employed in small open economies, where many regulations are local, despite nationally mandated guidelines. Examples of small open economies include some U.S. states, Canadian Provinces, and European regions, including all the Nordic countries. Application of these findings can result in industry specialization within global value chains, providing a way to success through international trade that will boost regional growth. The end result will be delivery of the best value for all concerned stakeholders.

Section I

The Market Structure

CHAPTER 1

BLUEPRINT FOR UNDERSTANDING COMPLEX HEALTH CARE SYSTEMS

Joel Shalowitz

1.1 Introduction

In any country, the large number of stakeholders generates a great degree of complexity. This chapter presents some initial definitions and two working models that will help the reader understand different health care systems, relevant stakeholders, and the effects of their strategic decisions on other elements of the health care marketplace.

While the theme of this book is health care technology development and particularly the commercialization of biotechnologies, it is important to begin with an understanding of the health care systems that use it and how this technology fits into the other elements of such systems.

We should begin by understanding some definitions. First, many people define health in terms of the absence of disease. Consider the Oxford English Dictionary (OED) definition of disease: "A condition of the body, or of some part or organ of the body, in which its functions are disturbed or deranged." Instead of this disease-oriented view, it is preferable to consider the World Health Organization (WHO) definition of health: "the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." Indeed, biotechnology is used not only to treat disease but also to prevent it. The World Health Organization also provides a comprehensive definition of a health care system as one that "...encompasses all the activities whose primary purpose is to promote, restore, or maintain health... and include[s] patients and their families, health care workers and caregivers within organizations and in the community, and the health policy environment in which all health related activities occur."

With respect to the purpose of this book, the way in which a nation defines health and its health care system has significant implications for how it invests in, regulates and delivers biotechnology. The definition also has management implications for such initiatives as project choice, possible intra- and international joint ventures/collaborations, and marketing tasks such as promotion, pricing, and distribution.

1.2 The model for understanding health care systems

Most approaches to understanding different health care systems rely on economic models that fail to include such important considerations as culture, politics, and population characteristics. Table 1.1 presents a framework that systematically incorporates these additional dimensions to help you understand how any nation organizes its health care system. To demonstrate the use of this framework, the explanation below presents some sample questions and comments for each numbered cell. While examples from many countries are included, because of the focus of this book, special attention will be given to Finland and the United States. Further, in order to encourage discussion and thinking about these issues, redundancy is built into the model, as will be obvious from some of the questions.

Table 1.1 Features of health care systems

Domains for analysis	Who pays?	How much is paid? (costs/ budgets)	Who/what is covered?	Where is care provided?	Who provides the services and products?
Political/regulatory/judicial	1.	6.	11.	16.	21.
Economic	2.	7.	12.	17.	22.
Social/cultural	3.	8.	13.	18.	23.
Technological	4.	9.	14.	19.	24.
Population characteristics demography and epidemiology	5.	10.	15.	20.	25.

Source: Shalowitz, J. in Kotler, P, Shalowitz, J. and Stevens, R: Strategic Marketing For Health Care Organizations: Building A Customer-Driven Health System. Jossey-Bass Publishers 2008.

1.2.1 Who pays?

Cell 1. Political/regulatory/judicial

The first question you can ask is: Where does the power reside to decide about payment for health care services and products? The answer depends on the degree of centralization or decentralization of the system. In the United States, except for strictly federal programs like Medicare, regulatory authority for health insurance resides at the state level. Even in countries with national health programs, there is often a regionalization of health care payment and delivery. For example, Canadian provinces and territories regulate their health insurance plans. (References to Canadian provinces below are also meant to include territories.) At the other extreme of local control, government run health care systems in Finland and Sweden are managed at the level of municipalities.

Another question concerns the extent to which the public or private sectors pay for health care. In the United States, private insurance companies are largely responsible for health care payments. Most of this private insurance is purchased through employer and employee contributions at the workplace. At the opposite end of the spectrum is Cuba, where the entire health care system is publicly financed. Between these two limits there are a large number of variations. For example, in Canada, private insurance can provide coverage only for products and services that are not furnished by the provincial health insurance plans. In Chile, employees have the option to use the mandatory tax on wages to buy into either the state-sponsored health insurance plan (FONASA) or a private insurance company (ISAPRE). In yet another example, workers in Argentina (who purchase their health insurance with mandatory payroll deductions that go to their respective unions) must use after-tax money if they want to enroll in a private insurance plan. In Finland, municipality income and property taxes account for about half of the health care funds. The second largest source of funding is Kela, a nationally funded, independent body that reports to parliament. Kela has the following health care responsibilities: distributes funds to municipalities to compensate for disparities in population wealth and health status; finances outpatient pharmaceuticals; and pays for occupational health services. In addition, the Finnish system is unusual in that Kela reimburses individuals for a portion of the costs incurred from obtaining private health care services.

In summary, the role of Private Insurance vis-à-vis Public Insurance can be classified as follows:

- Duplicate-Public and private systems exist in parallel and cover same benefits (Chile)

- Substitute-Private system replaces public system for certain population sectors (Germany)
- Complement-Private system provides benefits the public sector does not cover (Canada)
- Supplement-Private system extends benefits of the public sector in extent and/or payment (U.S.-Medicare)

Cell 2. Economic

The state of a country's economy can also determine who pays for products and services, shifting the balance between government and private sources, such as employers and individuals. For example, in the 1990s, when the United States economy was rapidly expanding, many companies provided rich health care benefits for their employees. During the subsequent economic downturn, however, these same companies shifted more of the responsibility for payment to their workers. If the public sector has been largely responsible for financing health care, during bad economic times it may withdraw considerable support, leaving individuals to shoulder substantial financial responsibility. Extreme examples of this latter situation are rural China and parts of the former Soviet Union. The opposite situation also applies: when the economy is performing well and health care costs are rising, government often looks to increasing individual payments or enhancing the role of the private sector. Because of current adverse economic conditions, health policy experts in Finland are considering the American model of high deductible health plans.

Cell 3. Social/cultural

The social/cultural characteristics of a country will ultimately determine the mechanisms and sources of payment. In essence, these factors shape a country's health care "mission statement." (See Table 1.2 for examples from the U.K., Canada, Finland, and WHO). It is noteworthy that although many countries have crafted such statements, the United States government has not. For example, contrast two publicly funded programs. The U.K.'s National Health Service is financed from general taxation with a set budget. On the other hand, payments for hospital expenses of the Medicare program in the United States are mostly paid from a fund derived from employer and employee salary-based contributions and have no explicit cap on spending.

Table 1.2 Different socioeconomic and cultural views of health care

1. According to Gordon Brown, U.K. Chancellor of the Exchequer (March 2002) taxation to fund healthcare is fair compared to:
   - User charges – "it does not charge people for the misfortune of being sick"
   - Private insurance – "does not impose higher costs on those who are predisposed to illness, or who fall sick"
   - Social insurance – "it does not demand that employers bear the majority burden of health costs"

2. Policy and administrative objectives for Canadian healthcare:
   - Public administration
   - Comprehensiveness
   - Universality
   - Portability
   - Accessibility
   - Efficiency, value for money
   - Accountability, transparency

   (*Canada Health Act and Commission on the Future of Health Care in Canada*, 2001 Romanow Report)

3. According to the Finnish Ministry of Social Affairs and Health:
   The main aim of Finnish healthcare policy is to prolong people's health and the lifespan of their functional ability. It aims to safeguard the possibility for everyone to enjoy a good quality of life, diminish health differences between population groups and reduce the rate of premature death. This demands that attention is paid to the health factor of all societal decision making. Health is integral to social policy.

4. Health System Goals According to the World Health Organization, 2000:
   - Maximizing population health
   - Reducing inequalities in population health
   - Maximizing health system responsiveness
   - Reducing inequalities in responsiveness
   - Ensuring health care equitably

It is often difficult to determine which dimensions of culture are the most important in shaping a country's health care system. For purposes of comparing systems, however, analyzing measurable differences in culture can provide some guidance about which other countries may provide practical models for adoption. The most useful framework for such measurement is summarized below according to Hofstede (2001).

- Power Distance: The extent to which the less powerful members of institutions and organizations within a country *expect* and *accept* that power is distributed unequally.
- Uncertainty Avoidance: The extent to which the members of a culture feel threatened by uncertain or unknown situations.
- Individualism/Collectivism: Individualism stands for a society in which the ties between individuals are loose: Everyone is expected to look after him/herself and her/his immediate family only. Collectivism stands for a society in which people from birth onwards are integrated into strong, cohesive in-groups, which throughout their lifetime continue to protect them in exchange for unquestioning loyalty.
- Masculinity/Femininity: Masculinity stands for a society in which social gender roles are clearly distinct: Men are supposed to be assertive, tough, and focused on material success; women are supposed to be more modest, tender, and concerned with the quality of life. Femininity stands for a society in which social gender roles overlap: Both men and women are supposed to be modest, tender, and concerned with the quality of life.
- Long Term Orientation: The fostering of virtues oriented towards future rewards, in particular, perseverance and thrift. Its opposite pole, Short Term Orientation stands for the fostering of virtues related to the past and present, in particular, respect for tradition, preservation of "face," and fulfilling social obligations. (Hofstede, 2001).

Since a detailed description is beyond the scope of this book, the reader should consult this source for further explanation. To demonstrate its utility however, consider the following two examples. Some American policy analysts advocate adoption of a Canadian model for the U.S. health care system; however, the two countries have substantial cultural differences. Particularly, the U.S. is distinguished from other countries as being the most individualistic nation. A pluralistic system with standard benefits is, therefore, is not compatible with American culture. (For other views of cultural differences between the U.S. and Canada (see Adams, 2003))

As a second example, while Finland looks to other health care models for reform, it naturally studies Sweden. These countries share a history (Finland was part of Sweden from the Middle Ages until 1809), language (Swedish is Finland's second official language) and structure of health care systems (as mentioned above, both countries base their healthcare systems at the municipal level). Also, in several cultural dimensions, Finland is similar to other Scandinavian countries. One important difference, however, is in the uncertainty avoidance index. Using this measure, Finland is very different from all other Scandinavian countries and is closer to Germany and Switzerland. If this dimension proves to be the most important

cultural feature with respect to health care, the implication is that Finland needs to look to these latter two countries rather than (or in addition to) Sweden for health care system model reform.

Cell 4. Technological

In this context, technology incorporates drugs, devices, and procedures that are used in health care settings. The two key questions we must ask are: 1) Who approves new technology? and 2) How closely are safety and efficacy evaluations combined with cost considerations in determining whether a technology is approved and used? For example, in the United States, the Food and Drug Administration (FDA) will determine whether a pharmaceutical is safe and efficacious. This decision is totally independent of whether or not there are many similar pharmaceuticals in the same class already available in the marketplace, whether the newly approved drug is much more costly than its competitors (given equivalent benefits) or both. Contrast the FDA approval process with England's National Institute for Clinical Excellence (NICE). NICE approves pharmaceuticals based not only on safety and efficacy, but also on cost-effectiveness. This disparity principally exists because, in the former case, the United States federal government does not directly pay for most pharmaceuticals, whereas the British government does have such fiscal responsibility. Even more recently, with Medicare's new system of payment for drugs (Part D), the federal government decided not to bargain directly with pharmaceutical companies.

In Finland, the approval process is typical of European Union countries. In the case of pharmaceuticals, individual member countries can evaluate and approve the technology (in Finland, this task is performed by the National Agency for Medicine) or the member country can rely on a review by the European Medicines Agency (EMEA). The one requirement, however, is that all EU biotechnology must undergo the EMEA review.

Once the technology is approved, who pays for it depends on site of use. For example, in the U.S., patients with private health insurance usually share the cost of outpatient self-administered pharmaceuticals with the insurance company; for inpatient medications, however, the insurance company pays the hospital a negotiated rate that includes those items. In Finland, since municipalities fund hospital care, inpatient technology use is their responsibility. Outpatient pharmaceuticals, on the other hand, are paid by individuals as well as Kela. Kela also reimburses patients for outpatient chemotherapy. Further, municipalities are responsible for medical equipment and home diagnostics such as glucometers. In most health care

systems, patients have some out of pocket responsibility for both outpatient services and products.

Cell 5. Population characteristics

Demographic and epidemiologic characteristics of the population will also determine who pays for products and services. For example, one of the key questions facing many countries is how they will care for their growing elderly populations. Who will pay for their care? How much will the elderly be expected to contribute themselves and how much will the public sector finance? While the U.S. is not among the world's most rapidly aging countries, "the proportion of the population aged 65 and over in Finland will rise more rapidly than in Norway, Sweden or the average EU country from about 2010 to about 2020." (OECD, 2005)

1.2.2 How much is paid?

Cell 6. Political/regulatory/judicial

In most countries, the political process is the origin of public health care budgets and fee schedules. Even in the United States, where most care is provided by the private sector, government-set global fees for hospitals (diagnosis related groups or DRGs) and per-service fees for physicians (resource based relative value scale or RBRVS) have been adopted by the private sector as benchmarks for paying those providers.

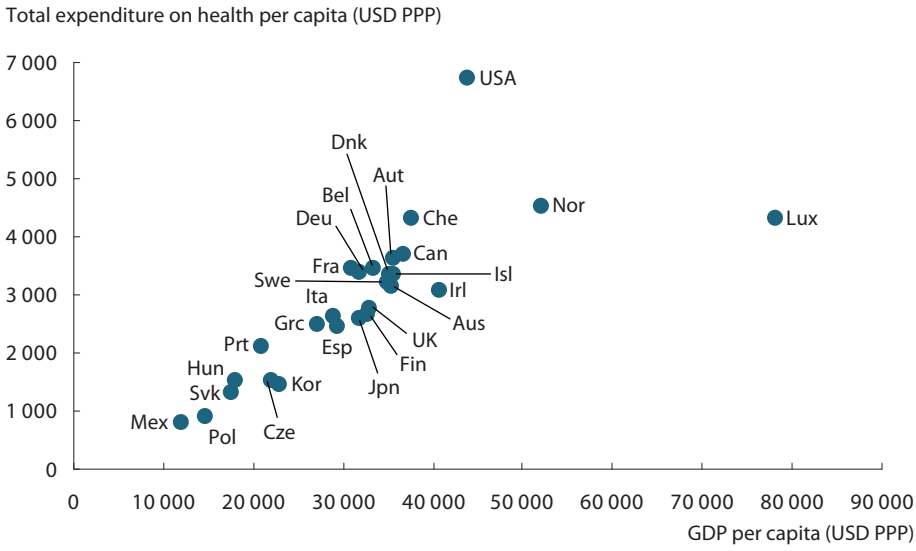
An example of judicial influence on costs comes from the debate on "grey markets" for pharmaceuticals;the practice of importing drugs from lower-cost countries into higher-cost countries. While this issue has garnered much press and Congressional attention in the United States (particularly with respect to importation of drugs from Canada), in Europe it has also been addressed by the EU courts, where such practices were found to be legal. In Finland, the municipalities have the legal authority to set patient cost sharing amounts, subject to Parliamentary limits.

Cell 7. Economic

Although politics will frame the debate about how much a country will spend on public programs, overall spending is most directly correlated with the state of a

country's economy. As shown in Figure 1.1, the gross domestic product (GDP) per capita is, by far, the single greatest correlate of a country's health expenditure per capita. The reason the United States is so far above the average per-capita health expenditures relative to its GDP is because prices are comparatively higher than in other countries. Luxembourg falls below other countries mostly because of its high GDP per capita. Another factor in this category is how much the government shifts payment responsibility to individuals. Not only do out of pocket amounts for each service vary widely by country, but so do the limits for how much an individual can be at financial risk. For example, in the U.S., an individual covered by Medicare has unlimited financial responsibility for health care expenses beyond those covered by that program. On the other hand, many countries put an upper limit on these amounts. For instance, in Finland, for 2008 the annual limit was €643.14. Usually the limits are defined by a person's total annual out of pocket expenses; but Japan, for example, sets monthly caps.

Figure 1.1 Health expenditure per capita versus GDP per capita 2006



Source: OECD Factbook 2008, OECD Health Data 2008.

Cell 8. Social/cultural

Given the political and economic determinants for health care budgets, the social and cultural characteristics of a country lay the groundwork for what is possible regarding such factors as the government's role in providing health care benefits, extent of government support, types of services covered by insurance (both public and private), and relative amounts of payments. As examples, in the United States, procedures are valued relatively more than cognitive services and hence are paid at higher rates. In Sweden, when the government realized a need for higher quality workers in the long-term care sector, it raised salaries.

Cell 9. Technological

As mentioned above, countries other than the U.S. consider the cost of technology along with its efficacy. Depending on the country, this cost analysis may occur simultaneously with the safety and efficacy evaluation or subsequent to it. Examples of some pharmaceutical pricing frameworks and cost-containment strategies are listed in Table 1.3.

Once the technology is approved and budgeted, its effect on health care costs can be determined by answering the question: How much does technology add to the cost of care as opposed to helping reduce overall expenses? One of the most significant factors contributing to rising health care costs across many countries is expenses related to new technology. This new technology is, by and large, "layered on" to the old technology rather than replacing it. A good example is balloon angioplasty and stenting of narrowed coronary arteries. These relatively less invasive techniques were supposed to replace many coronary artery bypass surgeries; in fact, the overall effect was to add a large number of patients who would not have been eligible for the latter procedure. Another example is positron emission tomography (PET scanners) for cancer staging. This diagnostic test, costing about USD 2,000, is added to computerized tomography (CT) and Magnetic Resonance Imaging (MRI). On the other hand, introduction of medication to treat peptic ulcer disease has all but eliminated surgery for that condition.

Cell 10. Population characteristics

Demographic and epidemiologic characteristics of the population will also determine who pays for products and services. For example, as mentioned above, one of the

Table 1.3 Reference/Index pricing

- Lowest priced identical chemical entity- active ingredient formulation, such as generics (generic referencing)
  Examples: U.S., Canada (some provinces), Sweden, Spain, Denmark
- Lowest price in therapeutic class (therapeutic referencing)
  Examples: Germany, the Netherlands, New Zealand, British Columbia
- Representative drug in class as benchmark for payment
- Market basket of prices from different countries
  Example: Canada (Patented Medicine Prices Review Board)
- Maximum price lowest of list of comparison countries
  Example: Brazil
- Total cost per time period comparisons
  Examples: Weighted Average Monthly Treatment Cost (WAMTC) in therapeutic categories (Australia, e.g., for ACE inhibitors, statins, CCBs, PPIs and SSRIs)
  Defined Daily Dose (DDD) cost of therapy, average cost within a category (Germany)
- Additional opportunity with pharmacist ability/mandate to substitute: Generic and/or therapeutic class
  Examples: Notify patient of generic equivalent, patient decides (Finland, South Africa and Slovakia): Mandatory substitution of lowest cost generic alternative (Sweden)

key questions facing many countries is how they will care for their growing elderly populations. Who will pay for their care? How much will the elderly be expected to contribute themselves and how much will the public sector finance?

1.2.3 Who and what is covered?

Cell 11. Political/regulatory/judicial

The political process plays a significant role in determining who will be covered and what health care benefits they will receive. For example, although all Canadian citizens are covered by government-sponsored insurance, the exact benefits vary by province. In the United States, examples in this category include state

laws (called *mandates*) that require health insurance companies to offer certain benefits to their members. Some of these mandates, such as infertility treatment and hairpieces for chemotherapy patients, stretch the limits of what traditional health insurance is designed to cover. In Finland, "the law lays down the basic nature and operating framework for the health care services, but does not concern itself with detailed questions of the scope, content or organization of services. There may therefore be differences in health service provision from one municipality to another."(Ministry of Social Affairs and Health, 2004).

Cell 12. Economic

In addition to determining the amount of money allocated for the health care system, the economic climate will also determine what benefits are offered. In good economic times benefits may be added, but during downturns even government benefits may be withdrawn. For example, because of financial pressures, in 2004 the Ontario government withdrew benefits for routine optometry, maintenance physical therapy, and chiropractic services under the Ontario Health Insurance Plan. In addition, increased premiums were levied because of these budget strains.

Cell 13. Social/cultural

These factors can have an important impact on whom and what is covered by public and private systems. For example, when economic conditions required benefit cutbacks in Germany, one of the most contentious programs that was eliminated was spa care – long a staple of that country's health care system.

Cell 14. Technological

The influence of technology in terms of coverage can be assessed by answering the following two questions: 1) What technologies are life saving, life enhancing, or lifestyle enhancing 2) How are these technologies prioritized? An example is the U.S. government's consideration of coverage for erectile dysfunction drugs when it designed the Medicare drug coverage plan. (After much debate, the government decided not to cover these medications.)

Cell 15. Population characteristics

Which populations require health care will also determine who or what is covered. The dilemma is: To what extent should the health care system focus on those with acute illnesses, those with chronic disease, and/or those who should receive preventive services? At this point, demographics intersect with epidemiology and "what is covered" needs to reflect population disease patterns. For example, according to the National Center on Health Statistics, the leading causes of death in the U.S. are heart disease, cancer and stroke. While these conditions are also important in Finland, the Ministry of Social Affairs and Health also lists alcohol-related deaths as a significant problem for both men and women.

1.2.4 Where is care provided?

Cell 16. Political/regulatory/judicial

Governments may enact laws to ensure appropriate access to health care. These laws can promote establishment of health care facilities (for example, by providing funding for community health centers) or restrict formation in areas of overabundance (for example, by imposing certificate of need requirements for hospitals). Other laws that affect access address portability of coverage across jurisdictions. For instance, the European Union's courts have confirmed the rights of its citizens to obtain health care across the borders of member nations. In Canada, portability of coverage is guaranteed by the Canada Health Act. Another way access is guaranteed is through mandates for treatment. In the United States, the Federal Emergency Medical Treatment and Active Labor Act of 1986 (EMTALA) requires that a hospital with an emergency department provide "an appropriate medical screening examination" to any patient who "comes to the emergency department" for examination or treatment. Further, the emergency department (and hospital, in general) must provide ongoing care until the patient's condition is stabilized. It is important to note that the patient's insurance coverage status is not a factor that hospitals can take into consideration in accepting the patient for treatment.

Cell 17. Economic

In countries with both public and private health care systems, during times of economic expansion, payers allow patients to receive care at and from nearly any

licensed facility and provider. During more challenging economic times, however, payers tend to be more selective about where patients can receive their care. The example that epitomizes this concept is managed care, whereby a select group of primary care physicians will provide and coordinate services for members of such plans. This principle obviously overlaps with the "who provides care" question below.

Cell 18. Social/cultural

These considerations also have a strong influence on where care is provided. For example, many communities want a local hospital, even though regionalization would make more economic sense with respect to economies of scale. Also, for cultural reasons, some populations are much less accepting of a trade-off between cost and site of care. Particularly in the United States, health insurers recognize that providing customers with freedom of choice of providers is an extremely important feature in marketing their plans.

Cell 19. Technological

In recent years there have been two opposite major trends in technology with respect to location. The first has been consolidation to a single site for services to treat highly complex conditions. These sites have been commonly called *centers of excellence*. The simultaneous contrary trend has been a move away from centralized locations to the point of care in the community. Technologies ranging from diagnostics to laser treatments have followed this latter pattern. In addressing the issue of where care is provided, one must also understand the extent to which technology enables care to be provided at "alternate" sites, such as in the home. A further trend is remote delivery of care, sometimes called *telemedicine*. Examples include consultations using audio and video conferencing over the Internet and treatments by robotic surgery. For instance, Helsinki University Central Hospital (HUCH) Neurology Department acts as the hub for the Hospital District of Helsinki and Uusimaa (HUS). If a patient with suspected stroke comes to another HUS hospital when a neurologist is not present, the specialist on call at HUCH can use a dedicated broadband connection to read diagnostic x-rays, visualize the patient and issue orders, all in real time communication with the local care providers. The result is enhanced timely diagnosis and treatment for a condition where minutes can make a difference in outcomes.

Cell 20. Population characteristics

With respect to the demographic determinants of where care is provided, one must also address questions about physical access to care. For example, how do health-impaired elderly get to regular physician appointments?

How are rural populations served when the closest health care facility or practitioner may be hours away? What is the role of telemedicine in providing care for the homebound and geographically remote populations?

1.2.5 Who provides the services and products?

Cell 21. Political/regulatory/judicial

The first question one must ask in this category is: What are the regulations and laws defining who is allowed to care for patients and to handle and prescribe such products as pharmaceuticals and medical equipment? Related to this question is the matter of the scope of such practitioners; for example, what are nurse practitioners and physician assistants allowed to do vis-à-vis physicians? International examples demonstrate a great variance: the U.S. medical community makes extensive use of nurse practitioners and physician assistants, whereas these professionals are absent from the clinical scene in Japan (the exception being nurse midwives). Another related question is: Who licenses these professionals? In the United States and Canada, such licensure is conducted by states and provinces, respectively. With increased globalization there is some pressure to make such licensure transnational. For instance, the European Economic Community Council Directive 93/16/EEC of April 5, 1993 states: "Each Member State shall recognize the diplomas, certificates and other evidence of formal qualifications awarded to nationals of Member States by the other Member States ... by giving such qualifications, as far as the right to take up and pursue the activities of a doctor is concerned, the same effect in its territory as those which the Member State itself awards." (Readers should consult the full document at:www.ilo.org/public/english/employment/skills/hrdr/instr/eu__5.htm)

Another major question in this category is: How is the supply of practitioners regulated, if at all? As an example, contrast the processes in the United States and Argentina for medical school admission. In the United States, admissions occur after a rigorous screening process; once students are admitted, however, few drop out. In Argentina, any student who can pass basic entrance requirements will be admitted to a public university, where tuition is free; however, the rigorous curriculum

leads to a much higher dropout rate than in the United States. Furthermore, the vast majority of medical school graduates in the United States go on to postgraduate residency training, whereas the numbers of such positions in Argentina are severely limited.

A related question is: Who accredits these training programs? In countries with public educational institutions, the government performs this function. In the United States, where most of these schools are in the private sector, there are a number of accrediting bodies that review the quality of training. Ultimately, the U.S. Department of Education is responsible for oversight of these accrediting organizations.

Finally, what is the nature of the laws and regulations governing anticompetitive practices and fee sharing? For example, in some countries it is perfectly legal and ethical for the referring physician to receive compensation from the specialist for sending patients. In the United States, this practice is considered both illegal and unethical. (This issue, of course, overlaps with the question of how much is paid.)

Cell 22. Economic

One could ask several questions to determine the extent economics influence who provides care. First, how are the fees for services and products determined, that is, are they set by government regulation, subject to free market factors, or a combination of the two? Within this payment structure, however it is determined, is there equity between practitioners? For example, are procedural specialists (surgeons) and cognitive specialists (primary care doctors) paid at equal rates for similar services based on such factors as time, risk, and skill? Also, how are non-physicians (such as nurse practitioners and physician assistants) paid compared to physicians for performing identical services? Finally, what is the role of the marketplace in determining the overall numbers of providers and their distribution both geographically and by specialty? In the United States, the marketplace largely determines the answers to these questions. In other countries, however, the government may have a more direct influence.

Cell 23. Social/cultural

The two principal questions in this category are: 1) How does a society determine and value who is accepted as a "legitimate" provider of care? 2) What are culturally valid treatments? For answers, one must look at who is allowed to provide nontra-

ditional health care services in a country and how much of the overall care fits into the category of alternative and complementary medicine. One can also ask if these nontraditional providers and treatments are regulated or if there is any oversight by the government. For example, traditional Chinese medicine is regulated in Singapore, yet, in the United States, many nutritional supplements and herbal treatments are not likewise scrutinized. Also, how does the society view the integration of traditional and nontraditional practitioners and the services they provide?

Cell 24. Technological

The primary question here is: How do decisions about technology adoption and use affect who provides care? To answer this question, it is important to know who designs the educational content for training providers and who gets to use the technology based on training, licensure, or certification. For example, in some areas, interventional radiologists perform peripheral angioplasties, while in other locations these procedures would be done by vascular surgeons. One must also know the process through which technologies are adopted, particularly when there is competition for resources. For instance, is the decision made based on population needs, return on investment, or political pressure from an individual or special interest groups?

Cell 25. Population characteristics

The summary question one must pose here is: How do demographic and epidemiologic characteristics of the population determine who provides the care? Answering this question requires an assessment of where the providers are located, similar to the earlier question regarding where the care is provided. One also must look at the demographic characteristics of those who are delivering the care. Finally, the existing and projected population characteristics will determine the needed specialty mixes. For example, the aging population requires more practitioners who perform colonoscopies (gastroenterology), cataract removals (ophthalmology), and other geriatric services. Likewise, if diseases such as HIV/AIDS or other widespread infections occur, practitioners in that specialty will be required. Next we will address how strategic planning can be applied to the above issues and how choices about multiple competing priorities simultaneously interact to uniquely define a health care system.

1.3 STRATEGIC PLANNING, HEALTH CARE STAKEHOLDERS AND THEIR VALUE PROPOSITIONS

One of the most important innovations in strategic thinking in recent years is a change from the notion of *selling* existing products and services to that of *understanding* and *meeting* customer perceptions, desires, and needs.

With respect to health care, the term *customer* refers to those who purchase a product or service after determining that its characteristics meet a need or desire. By comparison, a *consumer* is the one who actually uses the product or service.

A customer may or may not be a consumer. For example, a parent would be the customer for snack food companies while the child might be the consumer. The health care setting is a bit more complicated and we need more terms. Consider the following situation:

> A visiting aunt tells the mother that the mother's child looks sick and should be taken to a doctor (aunt = *influencer*). The mother decides to take the child to an emergency room (mother = *decider*). The child is treated by a physician (child = *patient*). The physician prescribes medication for the child (pharmaceutical company = *supplier*).The physician and hospital (physician and hospital = *providers*) notify the mother's health insurance company to pay for the service that was rendered (insurance company = *payer*) (Kotler et al., (2008)).

Further, consider that society as a whole might be interested in this transaction if it is for treatment of an infection that may spread to the rest of the population. Given these complex relationships, we need a term that encompasses all those persons and groups who have an interest in such matters as the funding, delivery, product development and receipt of health care services and products. We call all interested parties *stakeholders*.

Following identification of its stakeholders, a health care business will inevitably confront conflicting needs and wants. For example, both payers and patients are important stakeholders for pharmaceutical companies and health care providers. With respect to providers, just as health plans may impose unreasonable constraints on the delivery of patient care, patients can express unrealistic demands for the provision of medical services and products. Balancing conflicting stakeholder requirements is a constant and difficult challenge.

From country to country, stakeholders vary in such important dimensions as power and scope. For example, in Cuba, physicians are employees of the state-owned and run system. By contrast, in Japan, the Japan Medical Association is a politically powerful organization that includes private practitioners. Given these broad disparities in health system designs, a descriptive model of stakeholders must be appropriately flexible.

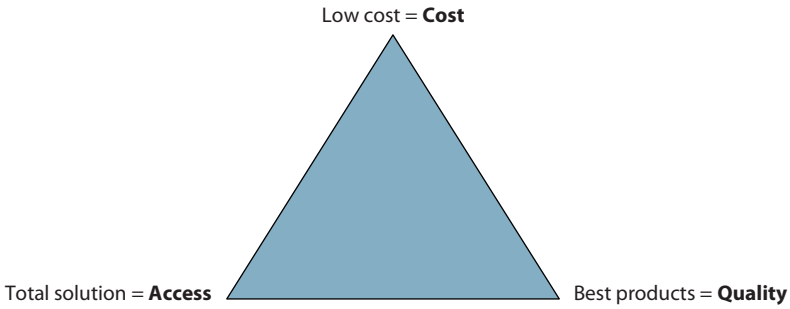
Stakeholders can be divided into three groups. The first set of stakeholders is individuals and their advocates in the private sector. Included in this group are not only the recipients of care (the "patient"), but also other individuals who have an interest in these patients, for example, family members, legal guardians, close friends, and community members. This category also includes private sector organizations that advocate on behalf of patients with similar characteristics, such as age, disease, or geographic location. For example, the Pediatric AIDS Foundation meets the first two criteria while the latter two describe the American Lung Association of Metropolitan Chicago.

The second stakeholder is the public sector. This sector can assume the functions of regulator, payer and provider. (It is very unusual for the government to act as supplier, though it does occur – such as vaccines in Cuba.) With respect to the payer and provider functions, it is important to note that *public programs are differentiated from one another by whom they cover for health care benefits*. Even in countries with universal coverage, separate systems of funding and care frequently exist for subcategories of the population, but usually include the elderly and the poor. Sometimes these categories are combined; for example, the Programa de Asistencia Medica Integral (PAMI) in Argentina covers the elderly and poor. These categories are exemplified in the U.S. by Medicare, Medicaid and government programs for those who serve it in various capacities, that is, active military, veterans, or government employees.

The third category of stakeholders is the private sector. *Constituents of the private sector define themselves by what they do*. The traditional division is among payers, providers, and suppliers. Payers include insurance companies, employers (who may self-fund all or part of employee health insurance), unions (the oldest form of health insurance and still the predominant method in Argentina), business associations, and charitable organizations. Pharmaceutical, biotechnology, device, medical supply, and diagnostic companies are significant producers of health care products. Providers comprise such categories as physicians, hospitals, nursing homes, pharmacies, and independent diagnostic facilities (e.g., laboratory and radiology).

Given these stakeholders, how can you formulate a strategy to address the needs of one or more of them? In other words, how can you develop a value proposition for your health care customers and other interested stakeholders? Before exploring the answer to this question, we must consider one more key term: *strategy*. We highlight three important characteristics of strategy. First, while businesses are often involved in many small, day-to-day decisions, strategy considers approaches to handling *major issues* with which the enterprise must deal now or in the future. Second, strategy involves setting the organizational direction for the medium to

Figure 1.2 Strategic choices to deliver health care stakeholder value



long-term. These timeframes are, of course, relative and vary by firm and industry. Third, useful strategies take into account that short-term decisions *do* need to be made. Strategy, therefore, provides a framework for making those decisions within the context of the organization's long-range goals. (Besanko et al., 2004)

While a number of strategic approaches exist for organizational and industry analysis, for example, SWOT (strength/weakness/opportunity/threat) analysis and Five Forces Analysis (Porter, 1980) the one used in Figure 1.2 provides a useful framework for understanding the health care industry.

This model posits that a successful company can choose to be excellent in only one of the three areas. In other words, there is a *tradeoff* when a company makes its strategic business choice. To be sure, the two dimensions not chosen as the strategic focus cannot be neglected, but they have a supporting, rather than a primary, function. For example, no one will buy a product just because it is cheap if it is very poorly made and does not solve a customer's needs. A brief explanation of this model will lay the foundation for its applicability to the health care field.

The low cost strategy is not just about pricing, but how it is achieved through operational efficiency and standardization. This approach and the customer tradeoffs are best illustrated by the globally ubiquitous warehouse clubs, for example, Sam's Club and Costco. These companies are supply chain experts who buy in bulk and stock stores in a standard manner. While many carry fine products, the selection is not based on best of category, but what is available at lowest prices. The same product may, therefore, not always be available at the same store. In order to keep costs down, these stores also limit personnel. If a customer wants low prices, what is sacrificed is a great deal of both choice and personal attention.

Examples of firms that focus on "best product" strategy can range from computer chips to fashion. Chip manufacturers are always trying to improve their technology and willing to leapfrog current products for new and better versions. Fashion firms constantly try to anticipate or shape new trends, again with the willingness to abandon old styles. However, fast chips and designer clothing do not come cheap. Nor do they offer a great deal of choice. Chanel dresses and Hugo Boss suits are high quality, but are expensive and do not come in all styles and colors.

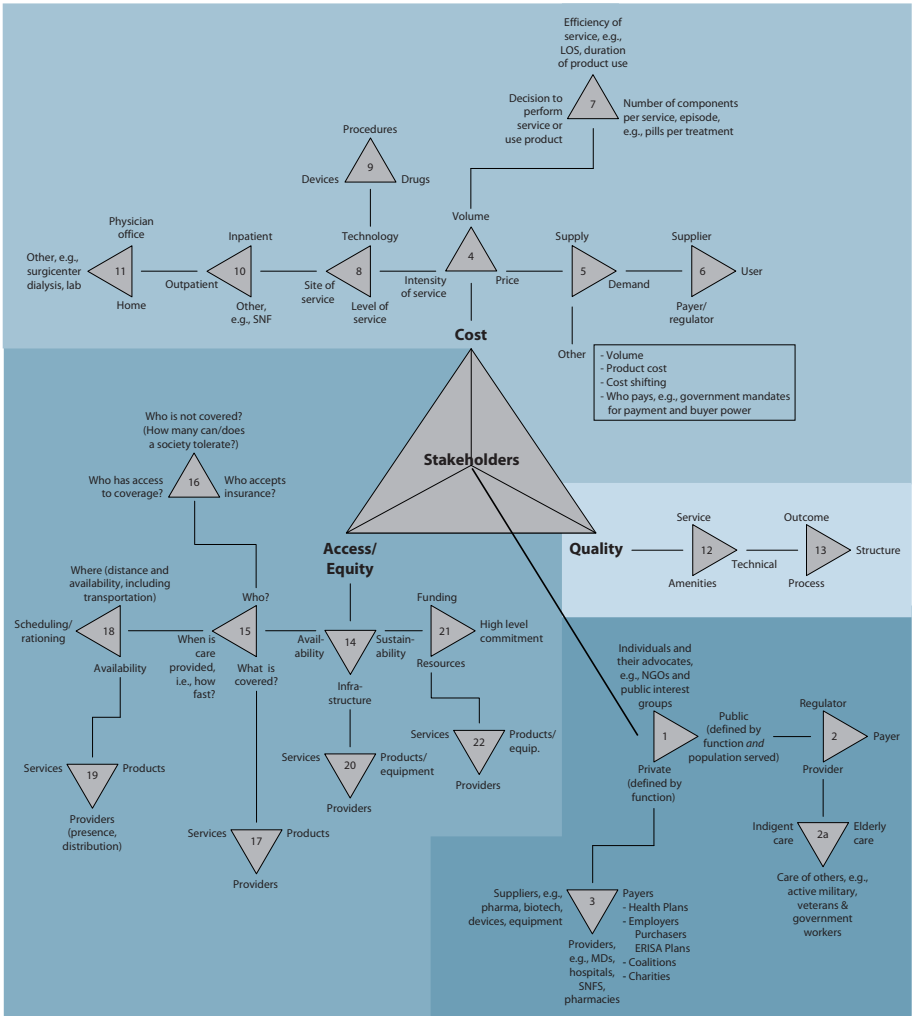
Consulting or personal service companies provide good examples of "total solution" strategies. For example, a customer may ask consultants to provide analysis and recommendations for an information system. The consultants will frequently recommend software and hardware, as well as procedures for using them effectively and efficiently. Each product that they recommend may not be best of class, but together they will provide a compatible, integrated solution. Such custom services are also expensive.

What should be clear from these examples is that companies need to make strategic *choices*. They cannot be all things to all people.

How do these concepts relate to the health care field? For many years, academics and policy makers have recognized that a well-designed health care system should also involve tradeoffs among these dimensions. The word *should* is used instead of *must* because, more often than not, stakeholders are not willing to choose. They insist on having all three simultaneously, putting tremendous stress on the system and causing periodic crises. For example, in the U.S., health care is the most expensive in the world when measured by purchase price parity, spending per capita, and per cent GDP. Technology is readily available and is not rationed. Furthermore, as mentioned above, when the Food and Drug Administration (FDA) evaluates technology, for example, pharmaceuticals, cost is not a factor in the approval decision. What the country sacrifices is access by those without health insurance; the number of uninsured has been more than 40 million for much of the past decade. Countries with national health systems, like England, spend less money on health care, not only because the service prices are lower, but also because health care is budgeted along with other government programs. Also, government agencies like the National Institute for Clinical Excellence (NICE) incorporate cost into their analyses of technology approval. Although all citizens are covered by public insurance, the limited budget strains the system by constraining the supply of providers, thus causing long queues and reducing access.

If these tradeoffs were that easy to explain, health care marketing, strategy, and policy would be relatively simple; but each of these three characteristics must be further broken down into their components to fully appreciate them. The elements that define them can also require balance and tradeoffs, thus creating a cascade of interdependent attributes.

Figure 1.4 The healthcare stakeholders and their value propositions



Source: Shalowitz, J. in Kotler, P, Shalowitz, J. and Stevens, R: Strategic Marketing For Health Care Organizations: Building A Customer-Driven Health System. Jossey-Bass Publishers 2008.

After all these components have been explained, at the end of this chapter, a unified scheme will be presented. This scheme should be used as a heuristic device and not a rigid framework. For example, technology, which is presented in the cost section, could as easily be discussed under quality. Further, there is much overlap

and many interrelationships exist among elements of different sections; a true representation would, therefore, appear as a complex web rather than elaborations of three discrete branches.

1.3.1 Cost

The word *"cost"* means different things to different people. Accountants often define the term as the average expenditure required to produce one unit of output (goods or services). Economists frequently refer to marginal costs, the resources required to produce *the next* unit of output. This latter concept leads to some unusual statements like: "The true costs of nonurgent care in the emergency department are relatively low." (Williams, 1996).

The reason for debates over the cost of health care is that the definition of cost used every day is more practical: *an actual payment*, based on a listed or prenegotiated rate. The total cost of products or services is governed by the following relationship:

$$\text{Cost} = f(P, V, I), \tag{1.1}$$

where P stands for price of the service or product; V for volume, or number of units; and I for intensity of service or product. Two brief examples will illustrate the use of this formula.

- Each year, national pharmaceutical expenditures are announced and increases are attributed to three categories: increase in prices of existing drugs (Price), increase in use of existing medications (Volume), and introduction of new products or technologies (Intensity).
- On a more micro level, the total cost of a hospitalization for a patient can be broken down into: level of care, for example, intensive care unit versus a bed on a regular medical/surgical floor (Intensity); number of days (Volume); and price per day at different levels of care (Price).

Understanding these components can lead to important insights not only for making strategic decisions, but also for public policy. To check rising health care costs, one can address any or all of these elements; however, the political consequences of manipulating each are significant and addressing one without also confronting the other two is futile. For example, the U.S. government has been dealing with rising physician payments by lowering the prices for these services. Doctors respond by increasing volume or, more importantly, by increasing the technology applied to care. A specific illustration is that while a CT scan can adequately diagnose

some problems, a MRI is often used at a significantly higher cost. Also, imagine cost-control strategies that only deal with volume, that is, rationing care, or those that address intensity, for instance, by withholding new technology. Price reduction is obviously the easiest, short term tool for cost control; but without management of the other two components, overall costs can never be adequately managed. See Chapter 8 for a further discussion on solutions to this problem.

Each of these three elements can now be "deconstructed".

Price

Classical economics dictates that price is determined by supply and/or demand for a product or service. This principle is true for health care, but only to a point. With regard to *demand*, user (or customer) demand for goods can influence price but, in health care, that is not the whole story. Suppliers and providers can also manipulate customer demand by such measures as physician-requested visits. Recall from the discussion on stakeholders that one of the unique features of health care is the presence of parties in addition to those who supply the goods and those who consume them. Payers and regulators (such as governments) can also influence demand through such direct or indirect measures as rationing services and regulating pricing, respectively. *Supply* may also influence price, but it is not always subject to free market conditions. For instance, in many countries, supply is centrally regulated. As an example, some governments regulate such items as the number of medical school places and/or advanced diagnostic imaging machines.

In addition to supply and demand, *other factors* also determine the price of health care goods. At least four of these other factors are involved in determining prices.

- First is volume. As in other fields, volume discounts are often available; however, some goods do not display the usual volume or experience ("learning curve") relationships to price that, say, calculators or computers did. For example, coronary artery bypass surgery prices have not decreased commensurate with the experience and standardization of the technology.
- Second, prices are often linked to production costs. An example from the governmental domain (Medicare) illustrates this point. The federal government determines physician prices based on computation of practice costs and the work that goes into providing the service. This method is called a Resource Based Relative Value Scale (RBRVS).

- Third, prices often have nothing to do with the item itself, but the other items consumed in the same setting. For example, one hears about such hospital charges as the USD 5 aspirin. Obviously, the aspirin's cost is nowhere near that amount, but other hospital services are often paid below production cost. This practice of cross subsidization is called "cost shifting." Some of these services are "loss leaders," like maternity care. Others services (like personnel-intensive disability evaluations) are truly underpaid, but the hospital must offer them in order to fulfill its mission of providing comprehensive care to the community. The price of a service or product can, therefore, depend upon factors other than just exceeding their acquisition costs.
- Finally, "who pays" can greatly influence the price, regardless of supply or demand. This category reflects "buyer power" as well as "non-market" forces. For example, Medicare has set its reimbursement for injectable pharmaceuticals at 6% over "average sales price (ASP)" and in-patient hospital payments based on the patient's diagnosis (diagnosis related group, or DRG). Providers cannot negotiate these rates.

Volume

Next is the *volume* input of cost. Determinants of volume can be divided into three components. The first portion of volume concerns the decision about whether or not to use a product or deliver/receive a service. While this notion seems simple, much debate has occurred over a variety of related issues in health care, prompting such questions as: Is the comprehensive "annual physical" really necessary for all adults? (The answer is: "No.)" (Laine, 2002) When is "watchful waiting" better than aggressive treatment? (One answer is certain cases of prostate cancer); and Are screening tests worthwhile? (The answer depends on the condition and the screening method).

An important related question is: Once experts agree that action is generally indicated (an exam must be performed, a test ordered and/or treatment administered), which among the options is the best choice? Obviously, choosing *one* may mean the other actions do not occur. For example, assume a patient has blockages in the coronary (heart) arteries that require invasive intervention. Is the appropriate action stenting or coronary artery bypass graft surgery (CABG)? Although the answer depends upon the extent of the blockages, where they occur and how many arteries are involved, experts may not agree on the best method for individual patients.

These examples and questions only deal with professional decisions. Patients and other stakeholders also determine whether or not actions are taken. For example, patients often pressure physicians for antibiotics for viral infections, when none are needed. Public interests also may determine whether something is done or not. For instance, in the past, England's National Health Service did not pay for hemodialysis for patients over age fifty-five.

Once the decision has been made to act, two further inputs will determine the overall volume. The first is the efficiency of its execution. For example, once the patient and physician agree surgery is an appropriate option, how long is the patient to remain in the hospital and how many resources are used for that episode of care? The second issue is the necessary number of units of care once a specific action is chosen. For example, there are various antibiotic regimens for treatment of certain bacterial infections, ranging from thirty pills (one pill three times a day of amoxicillin) to one dose of a liquid (Zmax form of azithromycin).

Intensity of service

The third determinant of cost is the *intensity of service*. This concept is used to refer to an overall episode of care as well as individual products used in its delivery. The first part of intensity is *level of service*. For example, does a hospitalized patient require intensive care or is a regular medical/surgical bed sufficient? Once the level of care is determined, the price and then cost will follow. Another illustration of this point is choice of antibiotics. Does a patient require a short course of oral medication or prolonged intravenous treatment?

Intensity of service also comprises use of medical *technology*, which consists of drugs, devices, and procedures. Sometimes these modalities are used in combinations, while at other times they are substitutes for one another. For instance, different preferred treatments exist for diverse heart beat irregularities. Some are best treated by medication (amiodarone, for example), others should be cared for by devices (implantable defibrillators or pacemakers), still others require surgery (where the source of the rhythm disturbance is surgically ablated). Each of these different technologies carries its own cost.

Finally, the *site of service* is an important determinant of intensity, and hence, cost. Sites of care can be divided into institutional and non-institutional settings. In the former category, hospitals come to mind first. The acute care hospital setting is referred to here as "inpatient" care. Other institutional settings consist of skilled nursing facilities (sometimes called SNFs) or long-term care settings, such as chronic ventilator facilities or long term care centers. We refer to non-institutional

sites as "outpatient" care. Common outpatient sites are the physician's office, the patient's home (with varying degrees of skilled home health care) and various other locations for freestanding diagnostic and therapeutic services. This latter category includes same day (ambulatory) surgery (whether at a hospital or free-standing surgicenter), dialysis facility, diagnostic laboratory, radiology facility, and physical therapy location.

The different types of sites can be substitutes for one another or appropriate sequential choices. For example, an elderly patient should be hospitalized for repair of a hip fracture. After this treatment she may recuperate and receive physical therapy in a skilled nursing facility and then be sent home with appropriate services there. On the other hand, the majority of surgical procedures are now performed on a same day basis, substituting for inpatient treatment. Furthermore, as mentioned above, many diagnostic and therapeutic technologies are moving from centralized medical centers to outpatient points of care. For example, many tests that were formerly only done in a hospital laboratory can now be performed with the same quality in physicians' offices.

1.3.2 Quality

The dimensions of quality can be divided into the amenities, service aspects and technical components. To illustrate and contrast these elements, consider a hospital stay.

- The *amenities* may consist of the items that form a first impression about the facility, for example, the building style, landscaping, and ease and cost of parking. While the marketing implications of these items are clear, these features bear no relation to the actual desired outcome, for example, success of a surgical procedure.
- The *service* aspects come closer to affecting outcomes. To continue the example, inpatient service may consist of meals, how quickly personnel respond to patient requests, and housekeeping services. While these functions support the actual business of delivering care and can more strongly influence opinions about the institution than the amenities, they are not part of the core activities in delivering treatment.
- The *technical* aspect is the work that is done that most directly affects outcomes. Examples of such activities are expertly performed surgery, choice of appropriate medication and skillfully administered nursing care.

The technical component can be further divided into structure, process, and outcome. Structure refers to those items that are either present or absent and usually

easy to measure. Examples include certification of specialists, presence of a piece of equipment, or adequate width of a doorway to accommodate a hospital bed. The meanings of process and outcome measures are self-explanatory.

1.3.3 Access and equity

The third part of this strategic tradeoff derives from the business model of providing a comprehensive, customer-intimate or total solution experience. This concept translates into the health care realm as issues of access and/or equity.

Availability

The first question regarding access/equity is whether certain resources are available. Availability can be assessed by answering the questions posed in 16 of Figure 1.3, starting with the question: *Who?* To expand on this inquiry: Who has health insurance coverage as well as who does not. These two issues, while apparently different sides of the same coin, address different strategic purposes. As an example of the former question, a pharmaceutical company will target the insured population for sales of a new product. The latter issue raises the question: How many uninsured people can society accept? In virtually all countries except the U.S., the answer to this question is: "None."

The third aspect of this dimension concerns who will accept the patient's insurance. For example, in the U.S., the joint federal-state program for the poor and other select populations (Medicaid) assures that eligible persons have at least a modicum of health insurance coverage. Unfortunately, this program often pays physicians so little and so late (nine month in accounts receivable aging is not unusual), that few may choose to see Medicaid insured patients. Also, not every commercial insurance plan will contract with every provider; patients must then seek those practitioners and institutions with whom their insurance companies contract in order to expect maximum payment for care. In most other countries, physicians can accept patients who pay with private insurance. Here again, however, not all physicians may accept the insurance and not all insurance plans pay for care by any physician.

"*What* is covered?" is the next question that defines availability. Even though an individual has insurance, not all services, products/equipment or providers are covered. For example, as mentioned above, in the face of budget pressures in 2004, the Province of Ontario cut routine optometry, chiropractic and physical therapy from the Ontario Health Insurance Plan benefits. As another example, most insur-

ance plans in the U.S. do not cover expenses related to prescription eyeglasses (they may pay for the professional exam but not the glasses themselves).

The third aspect of availability is *when* can care be provided. This timing depends on whether services, providers, and products exist and/or are close enough to patients to be useful. In some developing countries, certain technology and those skilled in its use may not exist. If it does exist, where it is located is extremely important. We not only refer to rural areas or developing nations, but also urban centers. For example, making free prenatal care available to inner city women is a futile gesture unless they have a way to affordably and easily get to these services. Finally, even if health care is close and easy to reach, some services are in short supply so they are explicitly or implicitly rationed. Queues in the U.K. for certain services are examples of this problem.

Infrastructure

In addition to availability, the two other dimensions of access that must be considered are *infrastructure* and *sustainability*. These two topics are of particular concern for developing countries, as well as rural and inner city populations in developed nations. While thinking about infrastructure can raise similar questions as the "where" and "availability" themes, this topic refers more to the *supporting roles* played by services, providers, and products/equipment rather than the primary activity or product. For example, think about a program to deliver immunizations to children in rural locations in a developing country. Assume that a pharmaceutical company donates the supplies and health care practitioners volunteer time to administer injections. The infrastructure dimension of this program includes not only the traditional items, like roads to get to needy populations, but also medical support services such as an information system that logs and tracks who received the shots and when they are due for booster immunizations.

Another example concerns HIV/AIDS. Supplying medication is necessary but not sufficient to successful treatment programs. The infrastructure must also include health care personnel who make sure patients take the medication as prescribed and are available for support when side effects inevitably arise.

Wealthy nations also have infrastructure problems. Consider the following examples. A hospital advertises an innovative program, only to find it cannot accommodate the volume of phone calls or schedule the service in a timely fashion. Shortly after a pharmaceutical company gets approval to market a new "blockbuster" drug, its production plants cannot keep up with demand; in the meantime, a competitor releases a substitute and garners significant market share. A producer of unique di-

agnostic equipment experiences quality problems in its factory that cause a lengthy cessation of manufacturing, reduced revenue, and a plummeting stock price.

Sustainability

Contemplating the infrastructure problem naturally gives rise to consideration of *sustainability*. Experts often use the metaphor that affecting lasting change in the health care arena is more like a marathon than a sprint. Sustainability starts with high-level commitment by appropriately empowered authorities. (While grass root activities are worthwhile, their purpose is often to convince decision makers to act.) Funding is also critical. University presidents are often reluctant to accept large donations for buildings because of the anticipated (and unfunded) ongoing maintenance costs. Similarly, in health care relevant follow up activities must be budgeted. Finally, decision makers and funders must commit appropriate resources for the long run. These resources must not only exist for episodic interventions, but also provide continuity.

1.4 Summary

In combining all these concepts a few other ideas emerge. First, consider that each stakeholder has different preferences among the cost/quality/access dimensions depending on the given issue. When two or more stakeholders are involved in a given matter, conflicts will often arise between them regarding balance of these options. The initial strategic choices that need to be made will, therefore, require answers to the questions: Who are the important stakeholders and what are their relative preferences? In answering this question, you must also understand where *you* fit into your stakeholders hierarchy.

Another important consideration is that when any one element in Figure 1.3 changes, it can have far-reaching effects on the entire system. For example, assume a state government lowers payment rates for physicians caring for Medicaid patients. How will that action affect the availability of physicians willing to care for those patients? As another example, consider a new diagnostic technology that can be used in the physician's office at the time of a patient's visit, providing quicker results. What are the implications of this test on volume, and hence cost, versus patient satisfaction?

In this chapter some initial definitions and two working models have been presented that will the reader understand different health care systems, the relevant stakeholders, and the effects of their strategic decisions on other elements of the health care marketplace. You are encouraged to think about how you can use these models in your sector of the industry and apply them when considering the material presented in the following chapters.

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CHAPTER 2

KNOWLEDGE HUBS IN THE GLOBAL BIOTECHNOLOGY INDUSTRY

Raine Hermans – Alicia Löffler – Scott Stern

2.1 Introduction

The previous chapter discussed ways to understand individual health care systems and also offered comparisons between systems based on such factors as culture and demographics. This chapter builds on those concepts by applying them to a global view of health care systems, with special focus on the biopharmaceutical sector (see also Hermans et al., 2008).

In order to strengthen the likelihood of success in their newly emerging hi-tech industries, nations have often provided financial and regulatory support. This support, however, has often been based on traditional ideas of clusters in vertically integrated value chains.

Findings presented in this chapter indicate that many countries around the world now "host" a biotechnology industry of varying importance and this activity within most countries seems to be highly localized in clusters. This clustered economic activity displays a strong reliance on and interaction with science-based university research. Further, limited data suggest that the number of biotechnology clusters that have achieved "minimum scale" has increased. Particularly in the U.S., the number of active clusters in biotechnology is increasing, both in terms of the number of distinct locations that serve as the host for activity in the industry, and of the size of spatial agglomerations. Despite these local projects, highly specialized functions of the value chains are being dispersed globally, since they can be performed less expensively in somewhere else. Particularly, start-up projects upstream in the value chain have been diffused across countries.

In addition to the need for pools of competent labor sources and proximity to academia, the high sunk costs of the biotechnology industry affect business strategies within the industry. Due to the long development processes there are high R&D costs in the industry, and these sunk costs can usually be covered only by the larger entities that can carry the risks of the most expensive phases of commercialization. This has led to a dichotomous market structure in biotechnology: there is a multitude of countries with a high number of innovative biotechnology startups, but fewer countries housing larger companies that can apply these innovations either in their production or by developing or marketing products based on the innovations.

While the international nature of many industries reflects the increasing availability of low-cost labor for many routine tasks, the globalization of biotechnology reflects a "catching up" process by a few regions around the world seeking to compete on innovation and specialized know-how.

2.2 Background

Biotechnology is a loosely defined industry that includes the commercialization of all life science innovations in the health, agriculture, and industrial sectors, commonly known as "red," "green", and "white" biotechnology, respectively. The industry emerged thirty years ago from the confluence of three major disruptive events: the development of recombinant DNA technology during the 1970s, a significant increase in federal and private funding for the life sciences, and the 1980 Diamond vs. Chakrabarty intellectual property case.

Traditionally, the majority of privately and publicly funded biotechnology enterprises, particularly those specialized in health care applications, have been located in the United States, specifically within a few geographic clusters also housing leading universities and other research institutions. North America has also been a leader in the commercialization of green, or agriculture-focused biotechnologies, largely due to the stringent regulation of plant-based biotechnologies in other Western countries, especially the EU. Industrial applications of white (i.e., industrial) biotechnology applications have been developed successfully by large multinationals headquartered in Denmark, and Japan has also commercialized such applications. However, in the last decade the commercialization of biotechnology has emerged as a key economic development strategy for regions and nations at all levels of economic and technological health.

This globalization is expected to affect the geographic distribution of economic activity in biotechnology, particularly in sectors with highly differentiated products that must undergo patent application processes. Such products are categorized by

high sunk costs and dense networks of intermediate inputs from supporting industrial and academic organizations.

The trends related to the geographic distribution of industrial biotechnological activity are examined in this chapter. Specifically, the following questions will be answered:

1. How are regional patterns within biotechnology affected by specific features of the field's innovation process?
2. What are the drivers of the geography of life sciences research and biotechnology?
3. How do those drivers have an impact on the "globalization" of biotechnology?
4. What steps could policymakers take to enhance the positive consequences of biotechnology in terms of regional development, consumer benefits, and general social welfare?

This chapter is organized as follows: The section immediately following provides a general depiction of biotechnology and the innovation process by which it is marked, along with the diverse trends influencing the field's development. Section 3 discusses frameworks and analytical tools for assessing geographic trends within biotechnology. Section 4 concerns empirical patterns of regional clustering in terms of innovative outputs. In that section some useful estimates for triadic patent families and regional specialization of biotechnology entrepreneurial activity are also provided. The chapter concludes with a section on policy implications.

Over the past decade, the biotechnology industry has been the source of increasing academic and policy interest as a potential source of regional and national economic development (Cortright and Mayer, 2002; Feldman, 2003). Though the current size of the industry is quite small (particularly in terms of employment), both local and national policymakers in the US and abroad have proactively encouraged local and regional investment in the biotechnology industry. In many cases, policy interest in biotechnology is based on the belief that while traditional sectoral sources of jobs and investment are increasingly subject to erosion due to globalization, the biotechnology industry is associated with superior wages and a high level of economic prosperity and growth (Battelle and SSTI, 2006).

2.3 The drivers of innovation in the biotechnology industry

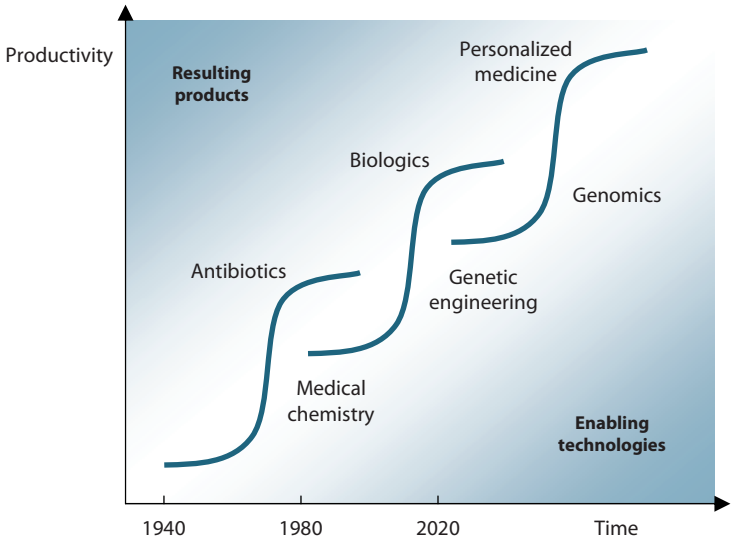
2.3.1 The origins and scope of the biotechnology industry

Biotechnology is a relatively young and still emerging sector of the economy, focused on the application of cellular and bio-molecular processes to develop, process, or make useful products (Biotechnology Industry Organization, 2007).[1] The origins of the biotechnology industry can be traced back to a confluence of technological, economic, and institutional shifts during the late 1970s and early 1980s: the development of recombinant DNA technology and other fundamental advances in life sciences research during the 1970s, a significant increase in funding and resources for life sciences research (both public and private, both in the US and abroad), and a set of policy decisions, such as the 1980 Diamond vs. Chakrabarty Supreme Court decision and the Bayh-Dole Act, that allowed intellectual property rights over innovations based on genetic engineering, even those funded by the public sector.

Since its inception, biotechnology has been constantly generating and adapting to new technologies. So far it has experienced four technology shifts over the last three decades alone (Figure 2.1). From the medicinal chemistry and pharmacology paradigms of the 1970s (which yielded a plethora of antibiotics and small molecule drugs), cutting-edge drug developers came to focus on biochemistry and molecular biology in the 1980s (resulting in recombinant DNA technology, genetically modified plants, biofuels, and therapeutic biologics) and genomics in the 1990s; a shift that hopes to make possible personalized medicine. A diverse collection of life, computational, material science, and engineering discoveries fuel these innovations. Specifically, biotechnology innovators stand at the confluence of many disciplines that emerge from academic and government laboratories, as well as commercial institutions. The structure of discovery and commercialization today is so interwoven that it is difficult to delineate academic from commercial institutions. As mentioned above, the boundaries of the industry are fuzzy, incorporating three related but distinct spheres: health-oriented, agricultural, and industry biotechnol-

[1] There is no single definition of the industry, and different criteria are often used defining the scope of the biotechnology industry in different countries. For example, the OECD employs both a functional definition – "the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or nonliving materials for the production of knowledge, goods and services." – and list-based definitions in which firms or workers are included in biotechnology if their activities fall within the scope of a set of listed categories (van Beuzekom and Arundel, 2006). To the extent possible, we are careful to define the definition and sample by which international or intranational comparisons are made.

Figure 2.1 Rapid innovation in the biotechnology industry is driven by a continuous flow of scientific and technological advances



ogy. At least in part because the geography of these three spheres is distinct from each other, it is useful to recognize some of the key differences between them.[2] Each will be considered in turn.

Health-oriented biotechnology

Private investment in health-oriented biotechnology has been concentrated in a small number of regional clusters, which are also home to leading universities and other research institutions. Publicly funded life sciences research serves as an extremely important source of discoveries for health-oriented biotechnology, and

[2] Health-oriented biotechnology has been subject to more detailed and intensive academic and policy analysis. In part, this is because this sector is the most distinctive in terms of the process of innovation and potential human impact. As well, starting with early analyses such as Kenney (1986) and Orsenigo (1989), health-oriented biotechnology has provided a useful industry setting to evaluate theoretical ideas in economics, sociology and related disciplines. See also Cockburn et al. (1999).

is widely dispersed across the United States (at thousands of universities, as well as intramural institutions and other research facilities). However, private sector investment in the health-oriented biotechnology industry is much more regionally concentrated, with historical centers in areas such as the suburbs of San Francisco, Cambridge, MA, and San Diego. Though the commercialization of biotechnology innovations has largely involved cooperation with more-established firms (many of which are located outside of these regional clusters), health-oriented biotechnology has been closely associated with academic entrepreneurship, whereby leading university research faculties are associated *with the creation of new biotechnology firms*.

Agricultural biotechnology

The United States has also played a leading role in the development and commercialization of "green," or agriculture-focused biotechnology products, particularly the development of new seed traits for staple and specialized agricultural products (from corn to papayas). While cluster-driven entrepreneurship has also played a role in this sector, the bulk of investment and commercialization has been centered around a small number of central players, including companies such as Monsanto and DuPont. While health-oriented biotechnology has a high level of visibility in discussions of economic development, agricultural biotechnology has faced significant resistance in international markets, most notably in Europe.

Industrial biotechnology

Relative to the other two spheres, white (i.e., industrial) biotechnology applications appear to be far more geographically dispersed than those of red biotechnology. By and large, industrial biotechnology has served as a useful source of process innovation in established industrial settings, and has been successfully exploited by large multinationals headquartered in Denmark, as well as Japan. Most recently, interest in biofuels and biotechnology solutions for the energy industry has greatly increased the level of focus and policy interest in this third sphere of the biotechnology industry.

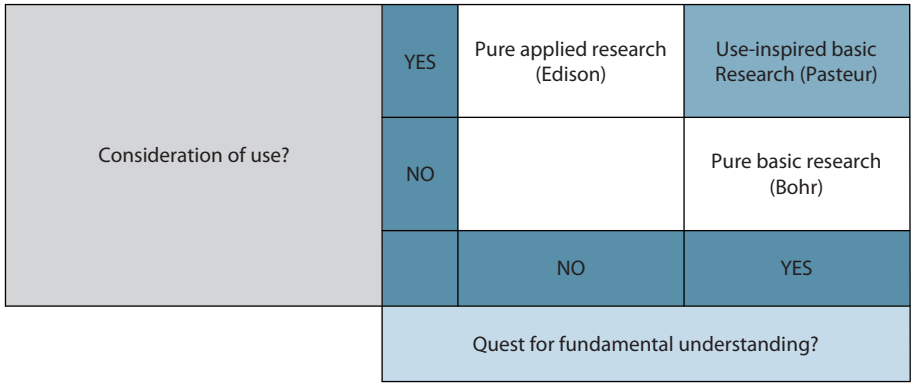
In the remainder of this section, some of the cross-cutting distinctive features of the industry will be emphasized, each of which will influence the ultimate geographic dispersion of activity within the industry.

2.3.2 The nature of biotechnology research

One of the most distinctive and pervasive characteristics of innovation in biotechnology is *duality*. Duality arises when biotechnology research makes a simultaneous contribution to both basic research and applied innovation (Rosenberg, 1974; Stokes, 1997). For example, the developments in recombinant technology and cloning in the 1970s or genomics in the 90s allowed scientists to understand the fundamental mechanisms of gene expression, as well as serving as novel therapies, diagnostics, transgenic crops, biofuels, etc.

The impact of duality is extensive, and undermines some of the implications of the traditional linear framework for science, technology, and innovation. While the linear framework allows for a concise formulation of the relationship between the nature of knowledge and the incentives provided for its production and distribution, it fails when knowledge has both basic and applied value.[3] Stokes (1997)

Figure 2.2 Pasteur's quadrant



Source: Adapted from Stokes (1997).

[3] In the traditional "linear" model, the norms and institutions supporting the production and use of basic versus applied research are separable and distinct. Under this model, applied research exploits publicly available basic research as an input, transforming that knowledge into innovations with valuable application. Though the linear model has been sharply criticized (Klein and Rosenberg, 1986), most formal theoretical and empirical economic research remains premised on the linear model, from assessment of the impact of university research (Jensen and Thursby, 2001; Zucker, Darby and Armstrong, 1998; Mowery et al., 2001; Narin and Olivastro, 1992) to the impact of Science and basic res earch on economic growth (Romer, 1990; Adams, 1990).

reformulated the traditional linear distinction between basic and applied research by highlighting the duality of research; a discovery could simultaneously have both basic and applied characteristics (Figure 2.2). Instead of placing research on a linear dimension ranging from basic to applied, it can move along two dimensions: in terms of whether they are dependent on "considerations of use" and, separately, on a "quest for fundamental understanding". Since its inception, biotechnology research has been at the center of Pasteur's Quadrant, and so individual discoveries both rely on and influence both science and commercialization.

The traditional "linear" framework fails when knowledge has both basic and applied value. Since its inception, biotechnology research has been at the center of Pasteur's Quadrant, and so individual discoveries both rely on and influence both science and commercialization.

This new framework has important policy, location, and human capital implications. For example, because biotechnology simultaneously offers the potential for fundamental scientific discoveries and commercial breakthroughs, traditional justifications for Intellectual Property Rights (IPR) and for the norms of Open Science become questionable (Murray and Stern, 2007).[4] While there are many questions surrounding the use (and misuse) of IPR in this industry, the availability of IPR allows start-up biotechnology firms to focus on the development of early-stage ideas, and contract with pharmaceutical, agricultural, and chemical companies for downstream activities, including manufacturing, marketing, etc. Some argue that IPR actually promotes a "market for ideas" by increasing incentives for disclosure (rather than secrecy) and encouraging the exchange and trade of knowledge.[5]

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[4] By its very nature, scientific knowledge is non-rivalrous, so the diffusion of that knowledge can serve repeatedly as an input into future knowledge production. Because intellectual Property (IP) can exclude follow-on researchers from exploiting scientific discoveries, the use of IP can undermine the process of cumulative scientific discovery. More precisely, in the absence of an efficient mechanism for gaining access to knowledge (e.g., through efficient licensing), IPR can be used to erect barriers that hinder the effective exploitation of the scientific commons. It has been argued that these restrictions can impact the biotechnology sector since the use of non-rivalrous knowledge can lower overall research productivity, leading to the so-called "anti-commons" effect. While traditional theory justifies IPR on the basis of enhancing incentives for innovation in the tradition of pure applied research, the anti-commons hypothesis posits that the equilibrium level of knowledge diffusion and subsequent research productivity may be declining in the use and restrictions imposed by IPR particularly for "use inspired basic research" or research with a high degree of duality (Heller and Eisenberg, 1998). Most notably, Heller and Eisenberg (1998) suggest that the assignment of IPR to basic research provides researchers with a control right to exclude others using that knowledge for the traditional purpose of cumulative knowledge production. In other words, when research incentives are already sufficiently high due to a high "quest for fundamental understanding," privatizing the intellectual commons imposes a "tax" on the use of that knowledge and may restrict the diffusion of that knowledge, with few positive incentive effects. Instead of raising incentives for discovery, the use of IPR over knowledge which has been traditionally associated with Open Science can lower the equilibrium level of research productivity.

[5] Merges and Nelson, 1994; Arora et al., 2001; Gans and Stern, 2000; Gambardella, 1995.

2.3.3 The biotechnology value proposition and the structure of the value chain

While the economic impact of the biotechnology industry is still quite modest (relative to say, the automobile industry), the potential global demand for biotechnology products is large, mostly driven by demographic trends reinforcing the underlying value proposition of biotechnology's products. Biotechnology growth is in part propelled by an expanding demand for innovations that can address the needs of a growing and aging world population. The promise of biotechnology to find solutions to some of the critical problems resulting from the population growth, from new medical treatments to improving the agricultural output to developing new sources of energy, creates a favorable environment for this sector. The world's population is not only growing, but, in aggregate, growing older.[6] As life expectancy increases a need to find new approaches to treat chronic diseases, characteristic of the aging, will intensify. Similarly, the need to increase the productivity and efficiency of agricultural products to feed the rising population is becoming a critical global issue where biotechnology can potentially offer important solutions. At the same time, rising global trade and travel, highly porous international borders, increased urbanization, and an uneven distribution of wealth are creating an optimum environment for the emergence of outbreaks of new infectious diseases with no available treatments.[7] The pressing need for new treatments is creating a great demand for biotechnology innovations. Likewise, global warming, caused in part by the population growth has intensified the need for finding solutions for alternative sources of energy. Industrial biotechnology could provide some means of producing environmentally friendly bio-fuels.

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[6] Demographic projections estimate world's population gains from 6.5 billion in 2005 to 7.9 billion in 2025 (The United Nations 2004). The greatest growth in total population is projected in the rising nations of China and India, whose populations are expected to benefit from improved socioeconomic conditions that and should drive increased needs for biotechnology innovations. The global population is also growing older. Individuals over age 60 represented 10.4% of the world's population in 2005; by 2050 this segment is expected to grow by 1 billion, with a total number representing 21.7% of a much larger total population. This trend will undoubtedly spur greater demand for new biomedical innovations and treatments worldwide. Today, America's the over-65 population consumes 40% of the nation'sUS biomedical output.products and is reasonable to expect similar trends worldwide. Persons aged 60 and over comprised 10.4% of the global population in 2005; by 2050 this component will amount to 21.7% of a much larger total population. By mid-century, the number of persons aged 60 and above will grow by 1 billion. The greatest advance is expected in the rising nations of China and India, whose populations will come to benefit from drug treatments and medical devices formerly available mainly to consumers in the U.S. and Europe. (Magee, 2005).

[7] Just consider the case that today, an infected person can carry a disease from almost any place on the planet to any other place in less than 36 hours, a disturbing fact made even more chilling when considering the threat of bioterrorism.

Despite these promising opportunities, the industry faces a series of distinctive challenges in translating innovations into commercialized products and services for global markets; at least in part, these challenges are a consequence of duality. Close inter-institutional collaborations in biotechnology contribute to the need for geographical proximity around centers of research excellence. Moreover, one manifestation of the complex networked relationship between biotechnology firms and other institutions is that many researchers in biotechnology not only work at the convergence of multiple scientific fields, but also at the boundaries of multiple institutions. Biotechnologists often need to have both scientific and commercialization acumen; they work for and with multiple organizations on any given day by contributing their expertise as required to the various stages within many institutions.

At the same time, while proximity to scientific and commercial knowledge led to the rise of concentrated geographic clusters for biotechnology innovations, the jobs created by the products of these innovations are far more dispersed. Since the biotechnology value chain is highly fragmented and capital intensive, the innovator can rarely afford to develop the inventions all the way to market. While there is geographic academic/industry confluence at the discovery stage, there is less so at the later stages of product development and distribution of the value chain, where most of the jobs are created (Figure 2.3). These later stages are dominated by the established pharmaceutical, chemical, and agricultural companies and are globally distributed.

Commercialization takes many steps, and, while there is geographic confluence between universities and start-ups, the value chain is both complex and fragmented. Product development in biotechnology is a long and fragmented process. For example, it is estimated that an agricultural biotechnology product might take 10 years to bring to the market and an investment of USD 50-200 million.[8] Similarly, a drug might take about 12 years and around USD 800 million.[9] The innovator rarely has the resources to bring the product to the market and out-license or sell their technology to a large pharmaceutical company, which can more feasibly undertake the most expensive development (i.e., approval) phases. The value chain is fragmented with smaller companies specializing at the innovation, discovery stages and larger companies specializing in the development and distribution stages.

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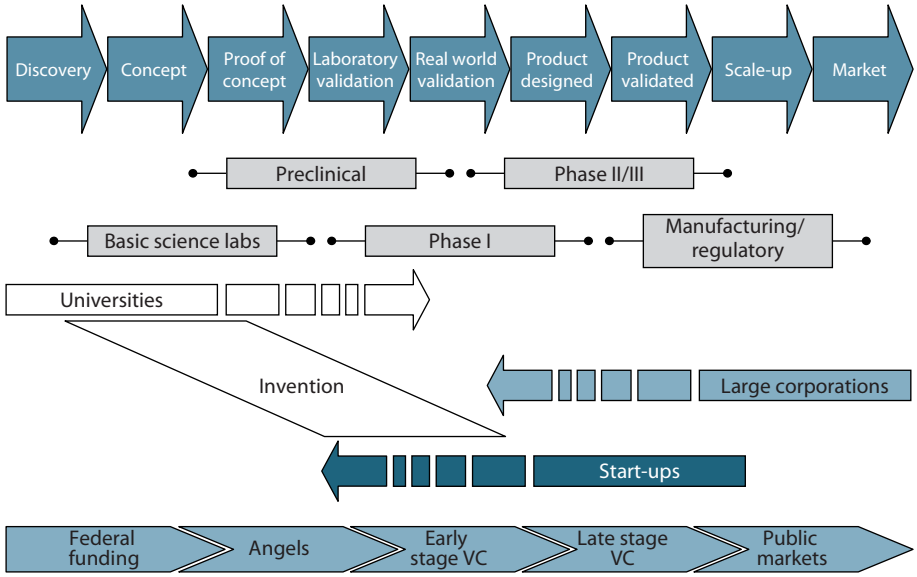
[8] McElroy, D. (2004): Valuing product development cyclein agricultural biotechnology. What is in a name? Nature Biotechnology 23. pp. 817-822.

[9] DiMasi, J.A. – Hansen, R.W. – Grabowski, H.G. (2003): The price of innovation: new estimates of drug development costs. Journal of Health Economics 22, pp. 151-185.

Figure 2.3 Typical value chain for a biotechnology product



Source: Adapted from Hermans, Löffler and Stern (2008).

This pattern of close connections with university and public researchers, as well as more geographically dispersed relationships with those that commercialize innovation have contributed to a highly entrepreneurial structure. This structure, combined with the presence of many revolutions in science and technology (as discussed earlier), has kept the industry in a state of "perpetual immaturity." The continuous flow of scientific innovations and the fragmentation of the value chain encourages the biotechnology sector to continuously create new companies. Since its inception, the biotechnology sector has around 1,300 companies in the US and around 5,000 worldwide (Burrill & Company, 2004). Although successful individual biotechnology companies grow large and mature, Genentech and Amgen being the prime examples, each with a market cap in excess of USD 80 billion, the sector as a whole is a study in dynamism, with new entrants appearing on the scene every year, attracting capital from both public and private sources. Once companies in the biotechnology sector establish a proven commercial path, they often consolidate or partner with established companies for development and distribution. Consolidation, however, does not result in a gradual winnowing of companies. This trend is offset by the continuous rate of company formation that keeps the sector fragmented.

The biotechnology supply chain is fulfilled by specialized players. Firms often do not integrate vertically and continue to play within specific and limited stages of the biotechnology value chain. Overall, the industry supports a highly dynamic structure, based on its foundation in rapidly emerging scientific disciplines, its potential to solve important issues and create significant value in health, agriculture, and industry, and in its orientation in terms of the commercial application of knowledge which is simultaneously of independent scientific interest.

2.4 The drivers of location and clustering in the biotechnology industry

The first part of this section deals with the geographic drivers of the biotechnology industry, an issue of particular importance given today's intensifying globalization. The discussion is based on the literature of international trade analysis, particularly with regard to the specific framework of Geographical Economics (Krugman, 1991; Krugman and Venables, 1995). In the next section the patterns related to the formation of Porter-type (Porter, 1990) regional biotechnology clusters are considered.

As mentioned earlier, the drivers of the geography of the biotechnology industry are complex and potentially changing over time. The geography of biotechnology reflects broad factors relating to the overall orientation of an economy to support innovative activity. As emphasized in the national innovation systems literature (and related work), broad-based policies and institutions serve as an important precondition for the location of innovative activity. Such policies and institutions include: an effective intellectual property system; the availability of high-quality human resources and risk capital; and institutions (and public/private partnerships) that encourage investment and innovation in particular regions.

However, while the common innovation infrastructure sets the basic conditions for innovation, the development and commercialization of new technologies take place disproportionately, in clusters, within geographic concentrations of interconnected companies and institutions in a particular field. For example, in the United States the biotechnology industry is primarily located in a few states and cities (Figure 2.4). A great deal of research has been devoted to exploring the drivers of cluster dynamics, and a rich literature documents the nature of clustering in biotechnology (Audretsch and Feldman, 1996; Audretsch and Stephan, 1996; Cooke, 2002; Hermans and Tahvanainen, 2006; Koput et al., 1996; Powell et al., 2005; Swann et al., 1998, and Zucker, Darby and Brewer, 1998).

Figure 2.4 Biotech clusters in the United States

The colored states indicate where there are both large and specialized firms in two of the three biotechnology subsectors (pharmaceuticals, research & testing, medical devices).

Source: The Brookings Institute.

Building on these insights into the geography of the biotechnology industry, there follows a short description of the global distribution of activity within the biotechnology industry. As described earlier, the industry grew out of a series of fundamental scientific breakthroughs in the 1970s, and was initially concentrated among a small number of entrepreneurial firms, mostly in the Bay Area in California and around Cambridge, Massachusetts. Since that time, the biotechnology industry has attracted great public interest, both for its potential in terms of innovation and human welfare, and for its potential as a driver of regional growth and prosperity. Despite interest in the future of biotechnology, relatively little attention has been paid to the current state of the biotechnology industry, in terms of regional patterns of employment, investment, and firm creation.

2.4.1 Drivers of globalization

The Geographical Economics framework (Krugman and Venables, 1995) within the literature of international trade analysis is based on Marshallian drivers used

to explain the location-related choices companies make. These drivers include technological development and spillovers, intermediate input connections, and labor pooling; we discuss each below.

High Sunk Costs of Technological Development: The Geographical Economics (Krugman and Venables, 1995) framework suggests that the initial stages of globalization primarily affect the geographic structure and distribution of economic activity. The decrease of trade barriers and the increased mobility of resources, such as knowledge, supports and strengthens agglomerations of economic and innovative activity. This is the case in sectors with dense networks between intermediate input providers and users, especially when there are high sunk costs in product development, implying the importance of scale economies (Krugman and Venables, 1995; Venables, 1996; Puga, 1999).

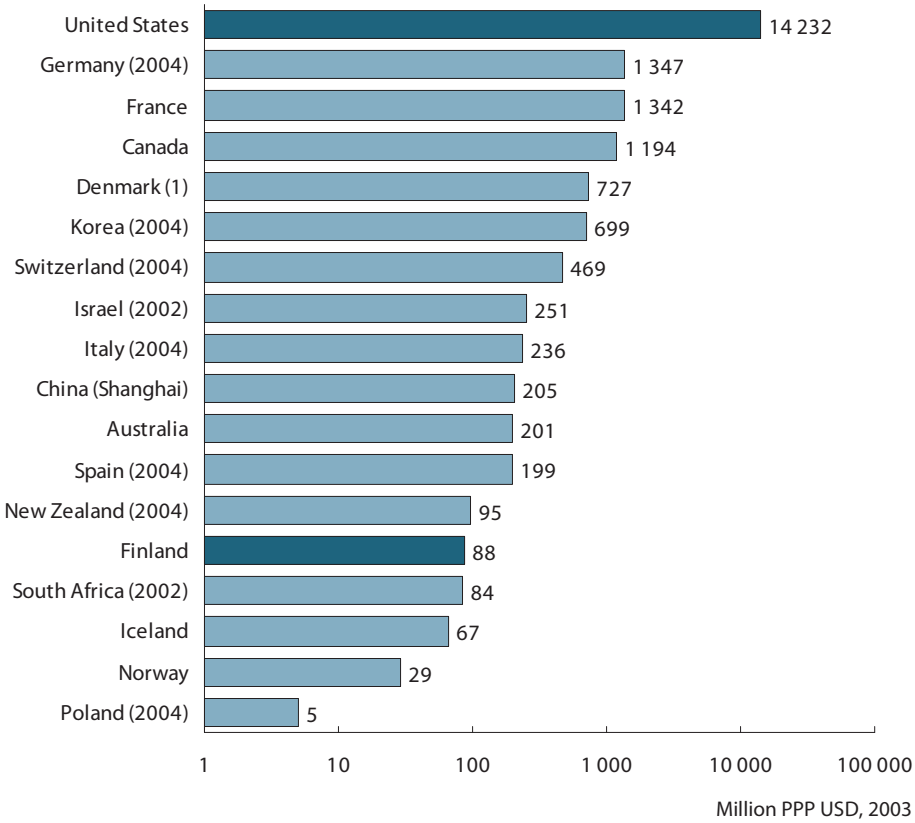
High sunk costs, such as large research and development expenditures, are a typical feature of biotechnology development projects, where R&D phases typically last over a decade. Once the product is taken to market, the realized sunk costs are offset by exploiting economies of scale, because the unit costs of production are small compared to the extremely high R&D outlay. For instance, DiMasi et al. (2003) estimates that the development of a new drug costs over USD 800 million. Thus most small biotechnology companies do not aim to launch the drug themselves, planning instead to out-license or sell their technology to a large pharmaceutical company, which can more feasibly undertake the most expensive development (i.e., approval) phases.

This might also be the case in other fields of biotechnological application: the commercialization of new biotechnologies in general is very time-consuming and financially challenging. For instance, reaching the point of first royalty income in commercializing forestry applications of biotechnology takes twice as much time as that in drug development, on average (Hermans, Kulvik and Tahvanainen, 2006).

Thus, according to the framework of Geographical Economics (Krugman and Venables, 1995) we expect that market structures typical of the biotechnology industry, high sunk costs and intensive collaboration networks, specifically, are drivers of an uneven geographic distribution of innovative activity within the sector. Figure 2.5 makes clear that the U.S. is a global biotechnology hub, based on its total R&D expenditure (i.e., highest sunk costs) within the industry.

Strong collaborative networks: The biotechnology industry is marked by highly active collaboration via networks that encompass companies and academic institutions. Due to the high level of sunk costs in this sector, spin-offs of academic institutions rely on external sources of funding to generate required cash flows for product development. This creates a strong connection between the biotechnology

Figure 2.5 Total expenditures for biotechnology R&D by biotechnology-active firms, OECD biotechnology statistics



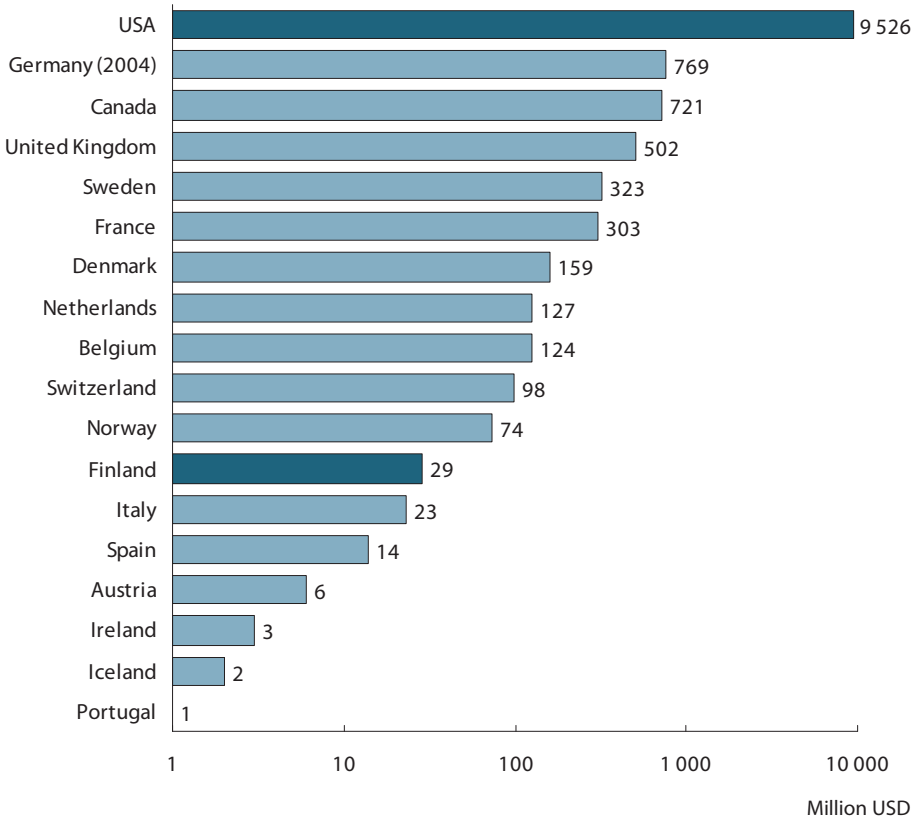
1. Results for Denmark could overestimate biotech R&D because a few health biotech firms did not give the % of their total R&D allocated to biotech. For these firms, all R&D was assigned to biotechnology.

Source: Van Beuzekom and Arundel, 2006.

startups and venture capital financiers. Thus the pooling of venture capitalists in a given region attracts biotechnology companies, and vice versa.

Human capital clustering and migration: Krugman (1991) analyzes the impact of labor migration on agglomeration dynamics. His analysis suggests that the larger the labor share in a sector employing increasing returns to scale in its production functions, the more probable the businesses within the sector cluster into geographic hubs, and thereby benefit from local labor pooling. While sometimes the

Figure 2.6 Total venture capital investments in biotechnology, 2001 to 2003 combined, OECD biotechnology statistics

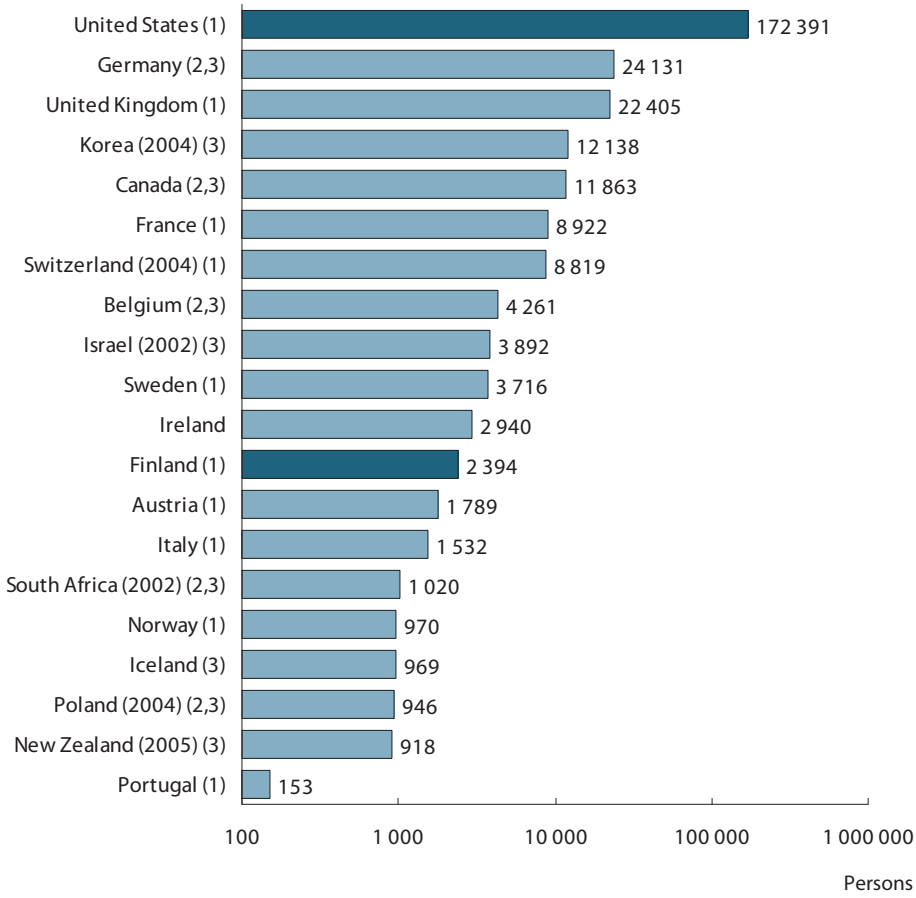


Source: Van Beuzekom and Arundel, 2006.

clustering will involve migration of personnel, in the biotechnology industry, it may involve an attachment to an organization in the cluster while maintaining a primary residence at the periphery. For example, a researcher at Johns Hopkins University (which historically has had difficulty interacting with entrepreneurs in its local environment) might have a relationship with a company in Boston or Silicon Valley in order to take advantage of the potential for commercialization in a strong cluster environment.

The U.S. employs over 172,000 individuals within the biotechnology industry, whereas the EU countries represented in Figure 2.7, employ 73,000. Based on these numbers, the geographic distribution of labor in biotechnology prohibits the

Figure 2.7 International labor distributions



1. Data from Critical I report to the UK DTI, 2005, basedon total employment in core biotechnology firms.
2. Limited to employees with biotech-related responsibilities.
3. Includes employment in both core and non-core firms active in biotechnology.

Source: Van Beuzekom and Arundel, 2006.

characterization of the field as a new labor-intensive industrial branch, because the share of labor in biotechnology remains modest relative to the global labor supply. Following this reasoning, biotechnology companies should be dispersed among very many countries and regions. However, the high mobility of labor in

biotechnology, and the industry's close link to academic hubs predict some level of geographic clustering.

Because of increasingly stringent immigration policies in the U.S., the number of international students has remained stable for the last five years. However, the student body profile is changing. While the fields of business management, mathematics, and computer sciences have experienced declines in international student enrollment, the number in the physical and life sciences has grown.

The number of international scholars (i.e., professors and post-doctoral fellows) is also increasing modestly in the US. In 2004 there were 89,634 international scholars at U.S. campuses, an increase of 8.1% from the previous year. Of those scholars, 21.5% are in biotechnology, almost double the proportion of 10 years ago. Thus the number of students, scholars, and high-tech workers based overseas has increased significantly in the last decade, contributing to a high level of biotechnology workplace diversity in the US. And this trend is expected to continue: during the last decade there has been a significant lobbying effort by the U.S. IT industry and the Biotechnology Industry Organization to raise the H1-B Visa cap. Depending on the region, between 6% and 10% of the US biotechnology workforce held H1-B Visas, with an estimated 18,000 nationally and a projected annual increase in need of 25% in some clusters.

Regional specialization: Krugman and Venables (1996) and Forslid and Wooton (2003) extend the Geographical Economics analysis to suggest that globalization may increase the regional specialization of industries utilizing economies of scale. Consequently, the biotechnology industry may specialize regionally by application segment or technology utilized. Accordingly, companies applying industrial biotechnology process techniques might form a different hub in a different location from those developing health care applications.

Table 2.1 indicates that health care-related applications represent the sector of biotechnology with the greatest share of labor inputs. Ireland is most skewed in this direction, with 83% of biotechnology workers in the health care sector. The proportion of biotech employees in this sector is also over 55% in all other countries, except South Korea, which has an equal distribution across health care, agro-food, and industrial-environmental sectors. Agro-food represents a relatively important application segment in South Korea, Israel, and Canada.

When we combine these statistics with those displayed in Table 2.1, we may conclude that the biotechnology industry as a whole does not employ as high a number of personnel as its more traditional counterparts do. Despite the relatively small number of workers in biotechnology, and thus lower gravitational pull for labor pooling, the global biotechnology industry seems to cluster around academic hubs in many regions. The dense collaborator networks and scale economies

Table 2.1 Percent of biotechnology employment by application: health, agro-food, and industrial-environmental sectors, 2003

	Health, %	Agro-food, %	Industrial-environmental, %
Ireland	83	3	7
Belgium	79	N/A	N/A
Canada	78	15	2
Norway	73	12	2
USA (2001)	70	4	6
France	69	4	4
Sweden	65	2	1
Germany	60	5	6
United Kingdom	59	7	4
Israel (2002)	55	23	8
Korea (2005)	36	29	31

Source: Van Beuzekom and Arundel, 2006.

thus facilitate the formation of these geographically concentrated and specialized clusters.

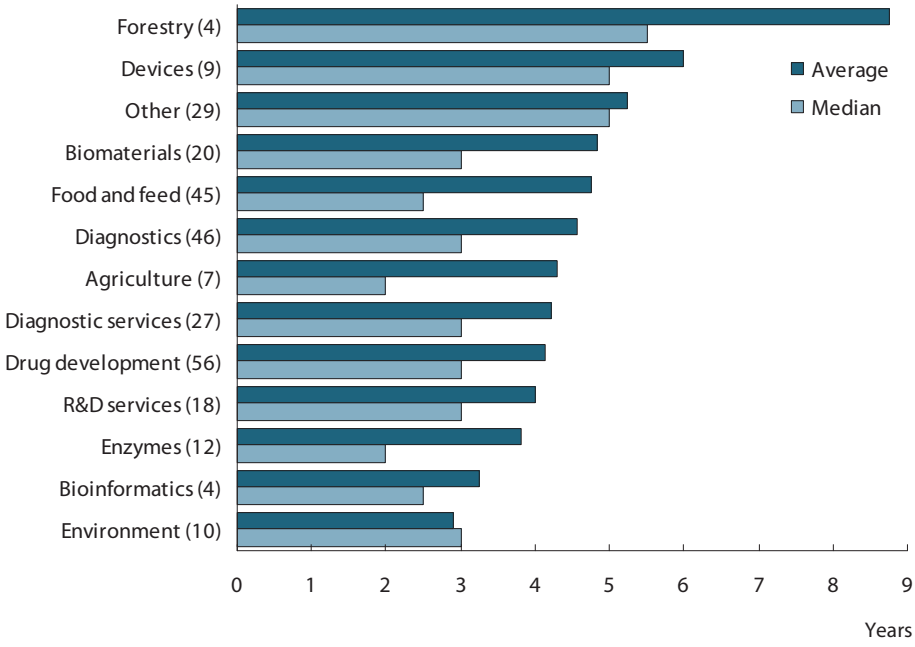
2.4.2 Differentiating sunk costs in distinct development phases

Sunk costs vary by R&D phase. As the R&D phase in the biotechnology sector is exceptionally long compared to those of more traditional industries, the conclusions of the Geographical Economics framework discussed above must be considered in this context. In this section contradictory models, each of which is insufficient by itself to explain the geography of biotechnology, will be utilized to draw further conclusions.

First the biotechnology companies are divided by their business logics. If the company aims to out-license its innovation at an early stage of research, it is active in a low-sunk-cost and biotechnology business marked by fewer economies of scale; whereas companies that develop their products to the point of market launch represent an industry with high sunk costs and greater economies of scale.

Figure 2.8 depicts average and median durations of commercialization within distinctive biotechnology application segments in Finland (Hermans, Kulvik and Tahvanainen, 2006). The median and average from-invention-to-sales durations range within distinctive application areas between 2-6 years and 3-9 years, respec-

Figure 2.8 From-invention-to-sales durations in distinct biotechnology application segments in an ETLA survey of Finnish biotechnology, number of product groups within the application segment in brackets

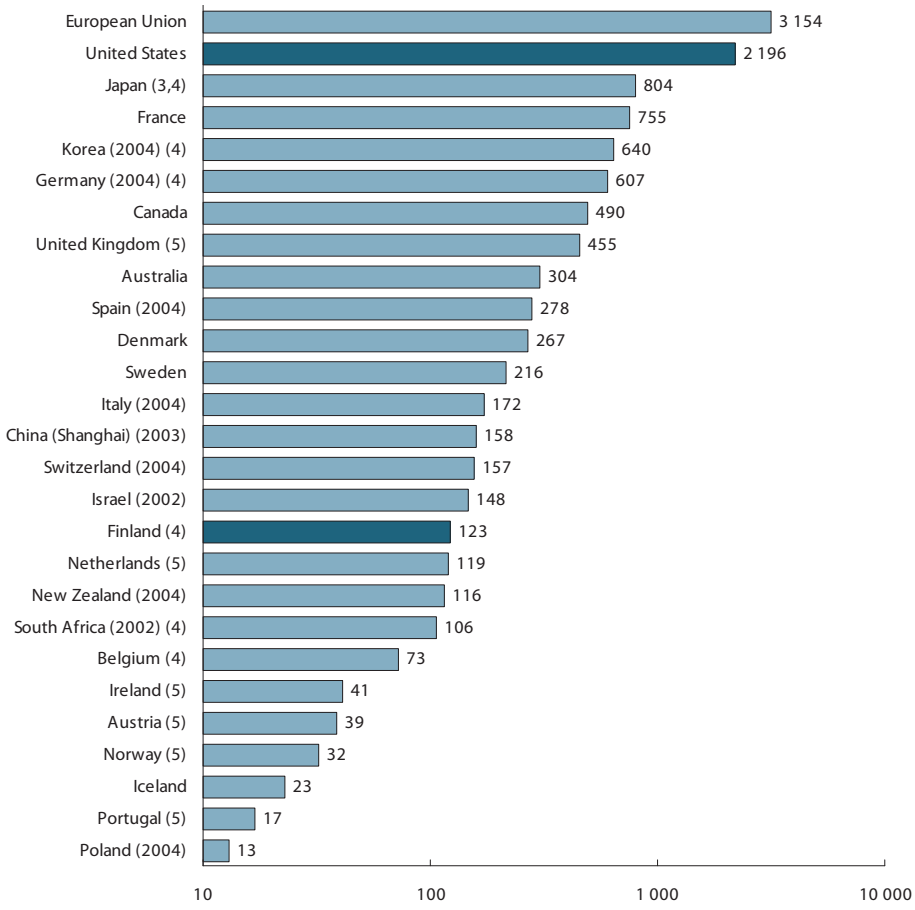


Source: Hermans et al., 2006.

tively. It is surprising that the average and median commercialization durations in drug development in the sample are even shorter than those within the food and feed sector and forestry. This implies that drug development companies implement technology sales or out-licensing strategies.

Because early stage drug discovery companies generate their sales primarily from out-licensing their technologies before the economically demanding clinical trial phases, the sunk costs of these start-ups are relatively low. The Dixit-Stiglitz (1977) type model of monopolistic competition suggests that low sunk costs should predict a high number of early stage (drug discovery and research) companies in this sector. The findings and reasoning above suggest not only a high number of early stage companies in the red biotechnology industry, but also their wide geographic distribution, which also seem to be the case for green and white biotechnology application areas (see Figure 2.9).

Figure 2.9 Number of biotechnology companies in distinct geographic areas



1. Excludes firms that only supply biotechnology equipment. In most countries biotech firms are defined as innovative, etiher performing R&D or having introduced a new biotech product or or process onto the market in the previous two or three years.
2. The definition of a 'core' biotech firm varies across countries, but is usually defined as a firm with less than 500 employeees and with biotech as its main activity. When no data are available for core biotech firms, the results are limited to all firms with some reported activities in biotech.
3. May include some firms that are only active in traditional biotech, but as far as possible firms that are only active in traditional biotech are excluded.
4. May include a few firms that are active in biotech but which do not develop biotech innovations.
5. Results from Critical 1 report for EuropaBio, 13 April, 2005.

Source: Van Beuzekom and Arundel, 2006.

As mentioned above, the drugs are usually passed through the most demanding (and expensive) regulatory approval phases by later-stage pharmaceutical companies. The Dixit-Stiglitz (1977) model implies that if the sunk costs involved with specific activities are high, one should expect the number of companies engaged in those activities to be small. In the pharmaceutical industry this is very much the case, especially with that sector's recent history of horizontal integration. Spatial implications also suggest that pharmaceutical companies might be expected to form strong geographic hubs independent of national borders and interests. But, as Markusen (1996) suggests, the large multinational companies could find it useful to locate their sales activity wherever they have markets. This trend might also apply to other biotechnology sectors if small companies out-license or sell their technologies and products to large matured companies that apply their products.

Table 2.2 Biotechnology R&D employees by countries, 2003

	Total	Per firm
United States (2)	73,520	33.5
United Kingdom (2)	9,644	
Germany (2004)	8,024	13.2
Korea (2004)	6,554	10.2
Canada (3)	6,441	13.1
Denmark (4)	4,781	17.9
France (2)	4,193	5.6
Switzerland (2004) (2)	4,143	26.4
Spain (2004)	2,884	10.4
Sweden (2)	2,359	10.9
Belgium	1,984	27.2
Israel (2002)	1,596	10.8
China (Shanghai) (4)	1,447	9.2
Finland (2)	1,146	9.3
Ireland (2)	1,053	25.7
Iceland	458	19.9
Norway (2)	283	8.8
Poland (2004)	109	8.4

1. R&D employment: includes scientists and support staff such as technicians.
2. Data from Critical 1 Report to the UK DTI, 2005 based on all R&D employees in core biotechnology firms.
3. Excludes firms with less than five employees or less than PPP USD 80,000 in R&D.
4. Full-time equivalents (FTEs).

Source: Van Beuzekom and Arundel, 2006.

According to the reasoning above, one might find that the market structure, or the number and size of companies, within the biotechnology industry might vary greatly. A hub should be characterized by a high level of business activity as a whole, as well as a larger average company size, which seems to be the case empirically: Table 2.2 suggests that the U.S. constitutes an overall hub not only in terms of total business activity, but also by demonstrating larger average firm size. This seems to be generally true of some geographically central countries with strong supporting industries, as well, including Belgium, Switzerland, and Ireland.

Domestic infrastructure: Martin and Rogers (1995) extended the Geographical Economics analysis to both intra- and international trade. By their reasoning, national public policies aimed at developing domestic infrastructure would attract companies to locate their activities in the country. This argument suggests that it would be fairly straightforward to use public subsidy programs to nurture an infant-stage biotechnology industry. However, at later stages of product development, when sunk costs are higher, it may be much more difficult to build an infant local biotechnology cluster based only on the possibility of attracting multinational companies. The next section extends the assessment of geographic drivers discussed above to a regional context.

2.4.3 Globalization at the regional level

Labor mobility seems to be higher within a country than that which takes place across international borders, but even higher within the U.S. than within European countries (Blanchard and Katz, 1992). This implies that some analytical tools related to labor mobility (Krugman, 1991; Puga, 1999) might be even more relevant to domestic contexts than to global ones. This section extends these analyses to assess domestic regional development in the era of globalization. Finally, geographic trends in biotechnology are discussed in the context of the industrial cluster framework.

Globalization and domestic regional development. Geographical Economics has also been extended to assess domestic regional structures affected by globalization. For instance, Monfort and Nicolini (2000) argue that globalization may lead to regional agglomerations within countries if there are labor migration barriers between the countries. In that way, biotechnology companies can exploit the domestic pooling of human capital and network with academic institutions, which can act as both input providers and sophisticated customers. This will increase local competition among innovative companies. These attributes of competitive advantage are discussed more thoroughly below and related to Porter's (1990) framework.

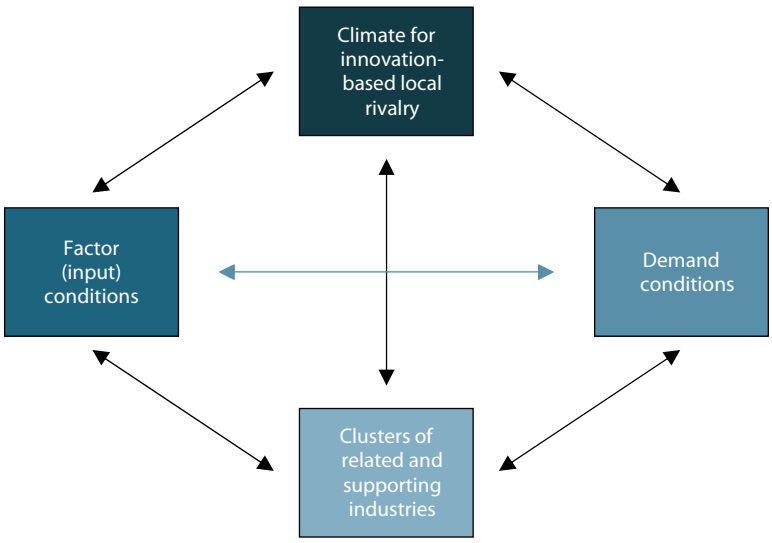
The spatial labor structure is more fragmented in Europe than in the U.S., where the largest geographical hubs have formed within a smaller number of regions. While the common innovation infrastructure sets the basic conditions for innovation, the development and commercialization of new technologies take place disproportionately, in clusters, within geographic concentrations of interconnected companies and institutions in a particular field. The cluster-specific innovation environment is captured in Porter's "diamond" framework (Figure 2.10), which suggests that four attributes of the microeconomic environment surrounding a cluster support its overall competitiveness and innovative vitality:

- The presence of high-quality and specialized inputs
- A local context that encourages investment and intense rivalry
- Pressure and insight emerging from sophisticated local demand

The local presence of high-quality related and supporting industries.

There are three primary drivers that relate the international trade literature (discussed earlier) to the geographic implications of cluster analysis: (1) A strong basic research infrastructure generates human capital pooling and forms the basis for the commercialization activity due to biotechnology's use-inspired basic research scheme (see earlier discussion of Pasteur's quadrant). (2) An ample supply of risk

Figure 2.10 The drivers of regional clusters



Source: Porter, 1990.

capital from either the industry itself or sources of venture capital is a necessary condition for cluster formation. (3) A high-quality information infrastructure is critical for capturing any technological spillovers.

Geographic clustering also promotes important externalities in innovation that are relevant to biotechnology. Thus, location within a cluster enhances a firm's ability to identify opportunities for innovation. Equally important, however, are the cluster-based flexibility and capacity to bring new ideas into reality. Within a cluster, a company can rapidly assemble the components, machinery, and services necessary for commercialization. Suppliers of essential inputs and "lead" buyers become crucial partners in the innovation process, and the relationships necessary for effective and efficient innovation are more easily forged among proximal firms. Reinforcing these advantages for innovation within clusters is basic pressure: competitive pressure, peer pressure, and customer pressure, all enabled by easy comparisons among clustered firms. The focus here is on clusters rather than individual industries, because of cross-industry spillovers and externalities vital to the rate of innovation.

As would be expected, the innovation environment of a cluster is fundamental to its competitiveness. For example, the Scandinavian pulp-and-paper cluster benefits from the advantages of pressures from demanding domestic consumers, intense rivalry among local competitors, and the presence of Swedish process-equipment manufacturers that are global leaders, (e.g., Kamyr and Sunds, for the commercialisation of innovative bleaching equipment). The Finnish pulp-and-paper industry utilizes specific biotechnological techniques in its production, which has motivated industrial enzyme providers to construct production plants in Finland (see Hermans, Kulvik and Nikinmaa (eds.), 2007). As a consequence, enzyme applications form the largest sales within the small and medium-sized biotechnology industry in Finland (Hermans, Kulvik and Tahvanainen, 2006).

As our theoretical framework above suggests, these industrial enzyme producers are diversified spatially and generally located within the highly specialized areas near primary customers, due to the customers' large production volumes. However, if regional policies are aimed at supporting peripheral R&D and production activity, the spatial distribution may be strongly affected. For instance, based on regional policies, R&D inputs may be distributed more evenly among centers and peripheries, but commercialized outputs according to the competitiveness and viability factors implied by the models above. See the box for a detailed discussion of the geographic distribution of biotech-related research inputs and sales outputs in Finland.

2.5 The geographic distribution of innovative output in biotechnology

This final empirical section moves beyond these general patterns of the geography of biotechnology to examine global patterns of innovative performance. Attempts to measure and benchmark innovative outputs have become common across advanced economies.[10] One approach to this activity (Porter and Stern, 1999; Furman et al., 2002) is based on a clear distinction between innovation output (specifically, international patenting) and its drivers: infrastructure, clusters, and linkages.[11] While *one must be very careful in* interpreting patterns based on patent data, patenting trends over countries and time are highly likely to reflect actual changes in innovative outputs rather than spurious influences, especially in measuring innovativeness at the global level. Also, patenting captures the degree to which a national economy is developing and commercializing "new-to-the-world" technologies, a prerequisite for building international competitiveness on a platform of quality and innovation. In short, international patenting is "the only observable manifestation of inventive activity with a well-grounded claim for universality" (Trajtenberg, 1990).[12] With that said, the analysis of international patenting in biotechnology comes with several important caveats. In particular, the standard for patentability for many biotechnology-related innovations differs across countries (and across time within countries). To cite but one example, as of 2006, the United States has granted more than 40 human embryonic stem cell patents, while the European Patent Office (EPO) has granted zero (as the EPO has been directed to reject human embryonic stem cells on "moral" grounds) (Porter et al., 2006). While US patent office practice has tended to allow patents relatively close to the arena of pure scientific "discoveries," EPO practice has tended to only allow patents when a specific industrial application has been identified. More generally, the use of patent data to identify the geography of

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[10] A review of this process is beyond this chapter's scope. However, a good starting point is the benchmarking programs of the European Union (http://trendchart.cordis.lu/).

[11] In addition to patent counts, there are some alternative measures to illustrate the distribution of biotechnology innovations. For instance, other forms of intellectual capital could also be useful to measure. On the one hand, some forms of human capital are often held as critical success factors in the science-driven business: for instance, outcomes of scientific research and a level of education and business experience of employees. On the other hand, the measures related to relational capital, such as collaboration networks, would be useful in assessing the significance of location of the biotechnology industry (Edvinsson and Malone, 1997).

[12] Trajtenberg (1990) provides a thorough discussion of the role of patents in understanding innovative activity, referring to their early use by Schmookler (1966) and noting their increasing use by scholars (e.g., Griliches, 1984; 1990; 1994). Our use of international patents also has often been used precedent in prior work comparing inventive activity across countries (see Dosi et al., 1990; Eaton and Kortum, 1996).

innovation is of course limited by the fact that many innovations (even important innovations) are not patented or patentable; while this critique is particularly important in the context of a broad cross-industry study, biotechnology is an arena with a close connection between innovation and patenting (Cohen et al., 2000). With these caveats in mind, there follows a detailed discussion of international patterns of biotechnology patenting.

Global biotechnology patenting. Several different measures are used reflecting the number of international biotechnology patents. In particular, the focus is on the number of patents granted to inventors from a given country by the United States Patent and Trademark Office (USPTO), European Patent Office (EPO), and the Japanese Patent Office. Next, these measures are combined in the analysis by examining the number of triadic patent families (i.e., patents granted in each of the three major patent jurisdictions).

Figure 2.11 graphs the number of biotechnology patents issued by the USPTO and EPO, by the region of origin of the inventor. Several striking patterns stand out. First, the United States is the dominant country of origin for biotechnology innovations, even those that are patented in Europe (i.e., where the "home bias" would favor the European inventors). Second, there was a sharp increase in US biotechnology patenting by US inventors during the late 1990s, a trend partially reflected in the EPO data and partially ameliorates from 2000 onwards. USPTO patents with European inventors are associated with a much more gradual rise, and achieve a 20% share of USPTO biotechnology patents by 2003.

Clearly, the regional patenting patterns reflected in the USPTO or EPO figures reflect a "home bias"; inventors tend to prefer domestic patent offices to foreign ones (this phenomenon is documented and discussed in detail in Criscuolo, 2006). At least in part, this indicates that domestic biotechnology companies tend to apply for patents first in their domestic patent office, and only seek foreign patents for their most significant and valuable products and processes. An attempt is made here to address the home-bias problem by moving towards triadic patent family counts to perform more strict comparisons among biotechnology patents filed in the USPTO, EPO, and Japanese Patent Office (JPO).[13] The patent families, or identical patents filed in all the patent offices, provide a more valid proxy for the economic value of patents. Patenting processes differ by country, and most companies or individuals will undertake the time-consuming process of filing a patent abroad only if the invention or process in question has significant earnings prospects.

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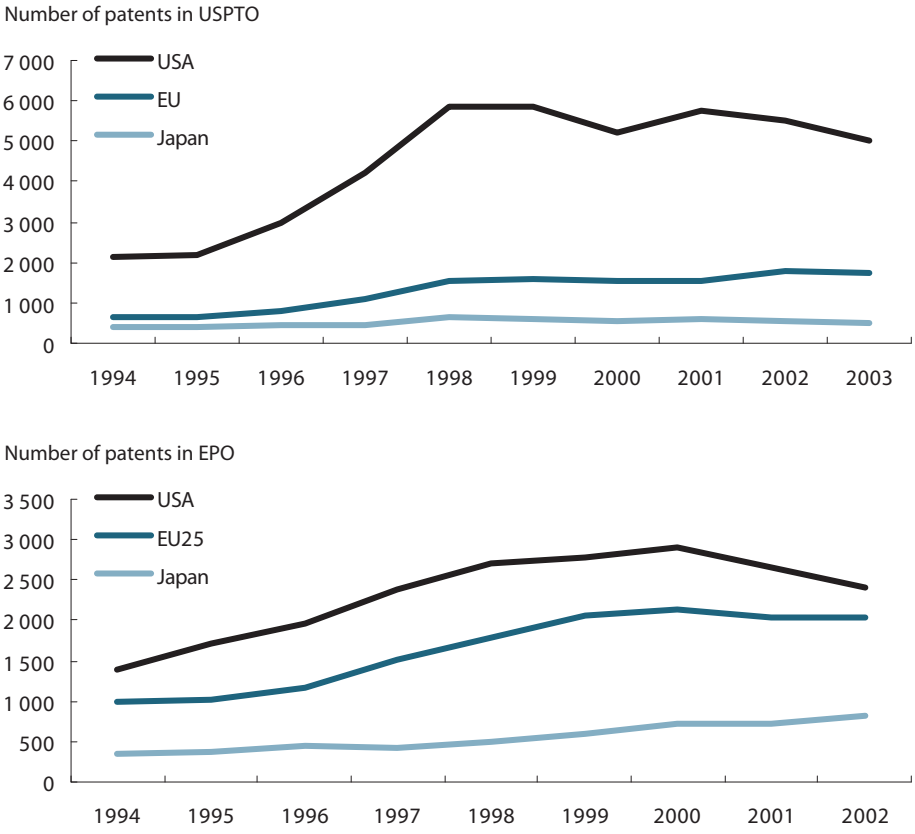
[13] Eurostat defines triadic patent families as follows: "A patent family is a set of patents taken in various countries for protecting a single invention... Patent is a member of a triadic patent family if and only if it is filed at the European Patent Office (EPO), the Japanese Patent Office (JPO) and is granted by the US Patent & Trademark Office (USPTO)."

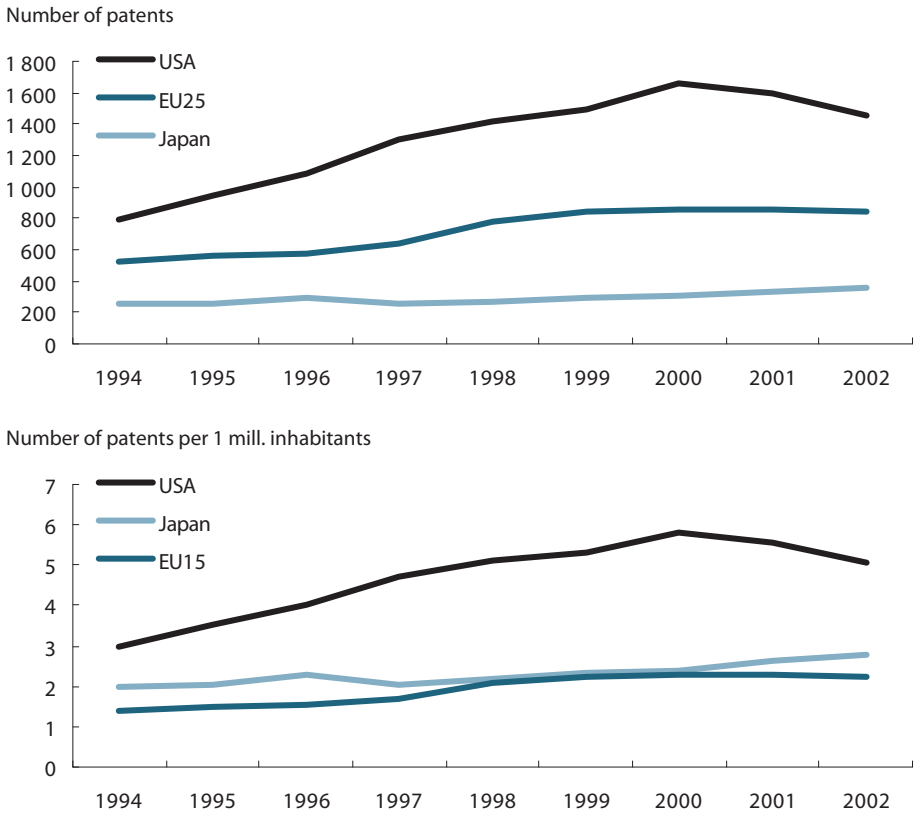
Figure 2.11 Biotechnology patent counts in USPTO and EPO by inventor's country of origin



Source: Van Beuzekom and Arundel, 2006.

Turning to triadic patent families in Figure 2.12, a similar set of patterns emerge. The United States continues to have a dominant share, on both an absolute and per capita basis. As well, when the patent-per-capita estimates are calculated, Japan's innovative productivity appears to be at the same level or higher than that of the EU. It is useful to note that, on a per capita basis, the U.S. has only about two times the innovative capacity of Japan and EU. Perhaps more importantly, these patterns provide some interesting insights into the evolution of the global biotechnology industry over the last decade or so. In particular, despite the fact that countries outside the United States started from a very low level (and so benefit from the

Figure 2.12 Triadic biotechnology patent counts and per capita measures by inventor's country of origin



Source: Van Beuzekom and Arundel, 2006 and authors' calculations.

"convergence effect" described earlier), the gap between the United States and the rest of the world has persisted. While there has been a very slight convergence in the very last years of the data (i.e. applications from 2000 onwards), these broad patterns are consistent with the hypothesis that regional agglomeration remains an important driver of the geography of the biotechnology industry.

Global biotechnology patenting by application segments. A more detailed analysis of innovative output as measured by patent counts, which are divided into 12 patent subcategories by the same regions considered earlier now follows. The analysis utilizes Derwent biotechnology abstracts, the most widely utilized classification

Table 2.3 Patent counts and share of patents in biotechnology patent classes 2000-2003

Patent class	Code	US	EU15	JP	Total
Genetic engineering and fermentation	A.	7,125 **58.7%**	2,671 22.0%	1,655 13.6%	12,138
Engineering – biochemical engineering	B.	196 40.9%	166 **34.7%**	103 **21.5%**	479
Sensors and analysis	C.	124 50.6%	77 **31.4%**	55 **22.4%**	245
Pharmaceuticals	D.	5,564 **60.2%**	1,978 21.4%	1,110 12.0%	9,250
Agriculture	E.	1,249 **62.1%**	391 19.5%	236 11.7%	2,010
Food, feed, and food additives	F.	260 12.1%	286 7.6%	186 9.0%	712
Fuels, mining, and metal recovery	G.	44 25.7%	66 **38.6%**	45 **26.3%**	171
Other chemicals	H.	160 31.7%	204 **40.5%**	176 **34.9%**	504
Cell culture	J.	1,058 **59.5%**	423 **23.8%**	249 14.0%	1,779
Biocatalysis	K.	593 37.0%	548 **34.2%**	492 **30.7%**	1,604
Purification – downstream processing	L.	54 42.5%	52 **40.9%**	16 12.6%	127
Waste disposal and the environment	M.	122 21.7%	185 **32.9%**	232 **41.2%**	563
Total		**16,375** 55.4%	**6,815** 23.0%	**4,433** 15.0%	**29,582**

Source: Derwent Biotechnology Resource (2006), Thomson Inc. (Thomson Reuters).

system for biotechnology patent analyses (Dalpé, 2002). Table 2.3 presents biotechnology patent counts and regional shares between 2000-2003, according to 12 distinct Derwent biotechnology resource classes.

In Table 2.3 the blue background indicates that a given geographical area (USA, EU15, or Japan) generates a higher proportion of the patents in an application area

than the country does on average in biotechnology.[14] For instance, 55.4% of biotechnology patents have been originally filed in the USA. 60.2% of the patents related to pharmaceuticals are filed originally in the USA, thus, the country is specialized in that application area in terms of the patenting intensity.

While the overall results reflect the more aggregate findings (i.e., the United States as a dominant player), Table 2.3 also reveals some striking differences across industrial applications. US leadership in biotechnology is centered on the patent classes most closely related to "red" biotechnology. More than 75% of all US patents are in *"Genetic engineering and fermentation"*, *"Pharmaceuticals"* and *"Cell culture."* While these classes are also important in the portfolio of the EU and Japan, these regions also register an important share of their patenting activity in classes in "green" and "white" biotechnology. These patt erns of comparative advantage can be seen most clearly when the share of patenting recorded by each region within each industrial application is calculated. Comparative advantage is here defined as simply those patent classes with a higher share of domestic priority than the country's share of the total number of biotechnology patents. For example, the United States has a comparative advantage (as indicated by the bolded entries) in the classes for which it holds over 55.4% of all granted patents. Consider, then, the areas of relative strength for the EU, such as *"Fuels, mining and metal recovery"*, *"Other Chemicals"*, *"Purification – Downstream Processing"* and *"Waste Disposal and the Environment."* These patterns seem to reflect historical strength by the EU in the chemical industry and related industrial applications of biotechnology. Similarly, the relative strength of Japanese inventors is apparent in areas such as *"Waste Disposal and the Environment"* and *"Other Chemicals"*. Indeed, it is useful to note that the EU and Japan both register a higher number of patents (on an absolute basis) in several application categories: *"Fuels, Mining, and Metal Recovery"*, *"Other Chemicals"* and *"Waste Disposal and the Environment"*. Finally, while the overwhelming bulk of US patents are in classes related to "red" biotechnology, the US also exhibits an advantage (relatively) in "green" biotechnology (the Agriculture sector), reflecting, in part, the leading global position of Monsanto and DuPont in this application segment. Overall, these patenting patterns suggest that US leadership in biotechnology is by no means monolithic. While the US does tend to have a dominating position in red

[14] The formal condition for flagging a quotient is $\frac{P_{ij}}{P_j} > \frac{P_i}{P_{total}}$, where P is number of patents, *i* denotes the country, *j* indicates the application area, and *total* stands for the entire number of biotechnology patents within the period 2000-2003 in Derwent Biotechnology Resource.

Table 2.4 From R&D activity to patenting and sales of the biotechnology industry

	R&D per capita index	Patents per capita index	Sales per capita index
USA	1.00	1.00	1.00
EU	0.37	0.41	0.28
Japan	n/a	0.46	0.45

Source: Van Beuzekom and Arundel, 2006 and authors' calculations.

and green biotechnology, the EU and Japan exhibit innovation leadership in areas related to white biotechnology. This is consistent with qualitative assessments that specific areas of biotechnology tend to be organized around clusters, with a small number of global innovation hubs.

From innovation activity to sales. Of course, the analysis so far only provides a limited perspective on the intensity of biotechnology activity across different regions: while evaluations of R&D employment and investment capture the intensity of R&D inputs, and patenting provides an imperfect measure of early-stage research outcomes, the ultimate impact of biotechnology ultimately depends on the ability to commercialize new technologies in the marketplace.

As such, the relative intensity of inputs and outputs of the biotechnology industry is briefly examined (Table 2.4). Biotechnology R&D expenditure, patent counts, and sales are divided by the total population within each distinctive geographic area to calculate per capita measures for each category, and then indexed to the US level (US = 1.0). Both R&D investment and patenting in the EU are approximately 40% of the US level (on a per capita basis), yet sales per capita are nearly a third lower (at 28% of the US level). As mentioned earlier, this may reflect the earlier stage of development of many European biotechnology firms, or perhaps the fact that European firms are more specialized in areas such as industrial applications that may be associated with a lower level of sales for a given level of innovative investment (and patenting output). In contrast, though Japan is also concentrated in white biotechnology, Japanese companies exhibit a slightly higher level of patent per capita than Europe (0.46) and a comparable level of sales per capita (0.45).

Country-Specific Innovation Performance. Finally, Table 2.5 presents the distribution of biotechnology patent counts across a range of countries from 2000 to 2003, divided by individual application areas. These data are not strictly comparable to the official OECD triadic patent counts presented earlier. Instead, Derwent Biotechnology Resources relies on an idiosyncratic algorithm for assigning patents (e.g., frac-

Table 2.5 Biotechnology patenting from 2000-2003 by country where a patent application was originally filed

	A. Genetic engineering and fermentation	B. Engineering – biochemical engineering	C. Sensors and analysis	D. Pharmaceuticals	E. Agriculture	F. Food, feed, and food additives	G. Fuels, mining, and metal recovery	H. Other chemicals	J. Cell culture	K. Biocatalysis	L. Purification – downstream processing	M. Waste disposal and the environment
WPO/IB	7,979	213	139	6,488	1	352	61	197	1,190	765	71	113
USA	7,125	196	124	5,564	1,249	260	44	160	1,058	593	54	122
Canada	111	6		90	36	3	2		21	10	2	9
Mexico	4			3	2				1			1
Cuba	1			1								
Argentina	5										3	
Brasil					1							
EPO	797	44	24	587	110	102	14	87	112	160	11	32
United Kingdom	653	21	16	520	93	22	6	15	99	67	9	23
Ireland	3	1		3	1		1		2			2
Germany	712	73	27	496	104	92	24	70	128	179	19	81
France	258	16	6	192	46	39	10	11	47	43	7	28
Netherlands	21	2	1	13	7	1	2	5	1	5	1	5
Belgium	4			3	1	1			1	2		1
Switzerland	10			7			2		2	4	1	1
Austria	17	3	1	14	4	2	2	3	5	9		5
Denmark	86	2		46	4		6	7	12	55		
Sweden	44		2	46	4			1	9	6	1	2
Finland	19	1		9	5	5		1		6		3
Norway	10			5			1					2
Italy	31	4		28	7	2	1	4	7	7	3	2
Spain	21			19	5	2			2	7		
Portugal	4			1		1				1		
Greece	1			1						1		1
Hungary	4			3	1					1		
Czech Republic	2	1		1						1		
Slovakia	1	1		1			1				1	1
Poland								1		1		
Serbia and Montenegro	1											
Republic of Macedonia		1										1
Russia	33	1		28	1	6	2		3	4	1	1
Turkey	1											
Israel	51	2	2	39	9				9	4		3
Japan	1,655	103	55	1,110	236	186	45	176	249	492	16	232
Republic of Korea	67	2	1	52	10	7	1	9	9	17		5
China	465	2	1	416	37	12		11	2	33	2	12
Taiwan	1				1							
India	6			4	4	1				1		
Singapore	6			2	4							1
Malaysia						1						1
Australia	146	8	2	111	42	6	5	2	22	2		5
New Zealand	23				14	1		2	2	1		1
South Africa	8	7			4					4		
Total	**12,138**	**479**	**245**	**9,250**	**2,010**	**712**	**171**	**504**	**1,779**	**1,604**	**127**	**563**

Source: Derwent Biotechnology Resource, 2006.

tional patent shares) to different countries, by the country of origin of the inventors (Derwent, 2006). With that caveat, the results are intriguing, as they deepen the broad patterns observed in the US-EU-Japan comparisons from above.

In particular, while this is not a detailed application-specific examination of individual countries, there seem to be several distinct "tiers" of global activity within the biotechnology industry. First, there are several countries that exhibit a high level of overall activity, realized across several different application areas. These multi-functional biotechnology centers include the United States, Japan, Germany, the United Kingdom, the Netherlands, and Australia. It is significant to note the presence of two relatively small countries, the Netherlands and Australia, in this category; both have strong histories of basic research in the life sciences, and have made significant investments in nurturing biotechnology companies and applications. Second, several countries have a slightly narrower base of biotechnology expertise, but are still present in several different application areas. These second-tier countries include Canada, Austria, Italy, Russia, and Republic of Korea (in the Table). Third, there are a several countries that are essentially specialized (but with strong relative performance) in a small number of application areas. These small open economies specialized in individual application areas include Ireland, Belgium, Switzerland, Denmark, Sweden, Finland, Israel, and New Zealand. Finally, a large number of countries have only a small number of patents in biotechnology, often exhibiting only one or two patents in a small number of application areas. These include several European countries (e.g., Portugal, Greece), most of the Latin American and former Eastern European countries, and several of the less developed Asian economies (India, Malaysia, etc).

Overall, these country-specific patterns reinforce several of the themes already mentioned. First, by a wide margin, the United States exhibits persistent innovation leadership in biotechnology. Second, an increasing number of countries around the world seem to be displaying significant activity within biotechnology, and there is significant heterogeneity among countries in their innovation intensity in biotechnology. For example, though Italy and Spain are at relatively high levels of overall economic development, both of these countries are clear laggards in biotechnology innovation. Finally, particularly as the biotechnology industry begins to spread from its origins in the life sciences sector, it will be increasingly important to distinguish the geography of innovation by individual applications; while the United States exhibits leadership in life sciences and agriculture, Denmark and Japan seem to have established leadership positions within industrial biotechnology applications.

2.6 Conclusions

In summary, biotechnology-based research and knowledge has both basic and applied value as shown by the discussion of Stokes' (1997) quadrant, and the links between scientific research and commercial applications are based on both the tacit knowledge based in human capital and codified knowledge in intellectual property rights. Further, this science-driven commercialization activity seems to have had a strong impact on the geographic patterns within the industry. For example, many startup companies prefer a location near research institutions with specialized knowledge.

In addition to the need for pools of competent labor sources and proximity to academia, the high sunk costs of the biotechnology industry affect business strategies within the industry. Due to the long development processes there are high R&D costs in the industry, and these sunk costs can usually be covered only by the larger entities that can bear the risks of the most expensive phases of commercialization. This has led to a dichotomous market structure in biotechnology: there are very many countries with a high number of innovative biotechnology startups, but fewer countries housing larger companies that can apply these innovations either in their production processes or by developing or marketing products based on the innovations.

There is active collaboration between the large companies that apply biotechnologies and smaller biotechnology developers. The collaboration takes place along a continuum from simple licensing contracts to equity-sharing arrangements between firms. Many governments have heavily subsidized the development of biotechnologies. However, the most successful commercialization activity seems to be associated with the presence of a larger traditional supporting industry infrastructure.

Health care-related biotechnology applications usually have the greatest market potential but also face the most stringent product approval process. Due to the nature of the development processes, the risk of failure is always significant, even in technically solid projects. Thus biotechnology application segments seem to differ in several respects. For example, their business logics and market structures can vary greatly, for instance, Monsanto dominates the field of agro-biotechnology, whereas there are many small drug-development companies, which serve as innovative input providers for larger pharmaceutical companies. Additionally, multinational pharmaceutical companies may seek to collaborate or even take over smaller but promising biotechnology projects. And industrial biotechnologies provide new technologies to their customers in traditional industries, both to improve the productivity of their processes and to develop novel products.

In absolute terms the U.S. leads the patenting race in both pharmaceuticals and agro-biotechnology. Today some companies have even grown from small biotechnology firms into highly integrated pharmaceutical giants (such as the U.S. Amgen). In agro-biotechnology, Monsanto is dominant. In white biotechnology, the Danish-based enzyme producers Danisco (merged with Genencor) and Novozymes hold half of the global market share, though Japanese and Korean producers are gaining ground.

In regard to innovation policy, some of the trends described above can be taken into greater consideration. The empirical results above and analysis provide a framework for assessing geographic trends among distinct biotechnological application segments. The U.S. is a clear global leader in red biotechnology, but lags behind the EU and Japan in commercializing industrial applications of white biotechnology. This can be understood in terms of comparative advantage, as presented earlier. According to a principle of comparative advantage these promising application areas of biotechnology should be further strengthened. Public policy could especially encourage the creation of applications aimed at reducing future health care costs. If new food materials or food additives could prevent common and/or cost-generating diseases, then agro-biotechnologies and some food additive relative industrial biotechnologies may be even more powerful tools than red biotechnologies in reducing the overall health care costs. These applications might provide a sustainable basis for technology and innovation policies to motivate public-private collaborations and location choices of companies.

However, the USA could act as a multi-sector hub in biotechnology, if the findings of Duranton and Puga (2001) are applicable in the international context. One could argue that innovation-related policies supporting white biotechnology, on top of the nation's already strong red and green sectors, might provide additional economy-wide benefits. White-biotechnology-based development projects could gain from the support of matured traditional industries both in business experience and direct financing. The huge domestic market potential provides a solid basis for developing new products in other segments. While it seems that new science-driven biotechnology companies have a limited ability to generate new jobs, biotechnology's links to more conventional industries might provide additional sources of U.S. competitive advantage and decelerate the industrial job transfer abroad. Additionally, the U.S. government's technology programs might serve the public good if they were aimed at reducing dependency on foreign energy suppliers, and promoting sustainable and low-polluting production processes.

Based on the discussions above (Monfort and Nicolini, 2000), a strong emphasis on all the distinctive biotechnology application segments would affect the nature of geographic clusters. For example, more specialized clusters might be associated

with academic hubs in those segments that rely heavily on scientific research. When biotechnological products are applied within the production processes of traditional industries, clustering may be based on the location of these customer companies, especially if the biotechnology inputs are not only technological knowledge, but also actual products (e.g., industrial enzymes).

In conclusion regions within continents, such as states in the U.S. and countries or provinces within the EU (or even within specific counties), might gain if they broaden the focus of their political interests away from health care related biotechnology innovation activity. The most sustainable innovation-based clustering could be achieved if the policies would be reconsidered by utilizing all four aspects of Porter's (1990) cluster framework: How can the competence base be utilized such that the most prosperous local industry is willing to support and utilize it? How can new biotechnology-based companies utilize the local marketplace to learn from the feedback of their most sophisticated customers? In what part of the value chain could innovative companies increase the value created by the supporting industry as well as their own?

Accordingly, regional technology-related policies might be most effective if they relate commercialization activity to the local academic competence pool, local industry structure, and customer base. Appreciating how biotechnologies are linked to a broad range of application segments will provide new opportunities to construct regional policies and corporate strategies. For example, who would have believed that tall oil, a substance generated in the pulp and paper production process, could serve in its advanced form as a cholesterol-reducing food additive with huge market potential and actual sales?

This assessment of international patenting activity revealed that countries with a highly developed infrastructure and large domestic markets demonstrate a higher overall level of patenting activity and greater diversity of applications than their smaller, or more peripheral, in terms of economic gravity, counterparts. This seems to be the case in the intra-country example, as well, where biotechnology business activity agglomerated to industrial centers, although the state had strongly subsidized the academic biotechnology research in peripheral regions.

The geographic peripheries in the intra-country analysis, then, seem to create a high number of smaller companies. This also seems to hold for international comparisons. Some geographically and economically central countries have the most viable biotechnology industry, led by the U.S., which also shows a high regional concentration of the most successful business activity. The EU, as a whole, shows a market structure with a higher number but smaller average size of biotechnology companies, but produces a large number of biotechnology patents.

Despite the high level of patenting activity in biotechnology, the industry is not associated with high production volumes and, in turn, large numbers of new jobs relative to other sectors. If this proves to be the case longer-term, trends in the biotechnology industry are not likely to have a significant impact on unemployment levels. Nonetheless, biotechnology will continue to generate major health-related and environmental benefits for society.

Appendix 2

Agglomeration of business activity: Spatial distribution of research inputs and sales outputs of the Finnish biotechnology industry

The information presented here is based on a study by Hermans and Tahvanainen (2006). An example of how the agglomeration patterns of R&D inputs and sales output differ in the context of a small open economy, such as that of Finland, is presented. The same spatial patterns have been observed in many other countries (e.g. Critical I, 2006).

To provide new insights related to the distribution of biotechnology-related inputs and outputs, and not just to the number of companies, the spatial patterns of employment, financial R&D inputs, and sales, that can then be related to the number of firms in each region, are examined. As such, it is possible to make conclusions about the true volume of business activities in the regions; relying on firm frequencies as a proxy for this information is a less sensitive approach.

It should be emphasized that the figures below are based on Finland's small- and medium-sized biotechnology enterprises (SMEs), and *exclude all large biotechnology companies*. The inclusion of large companies in the sample would render the results less meaningful, because such firms are outliers on several measures. For instance, some of the large Finnish pharmaceutical and food product corporations excluded from the analysis employ more than twice as many employees than the total SME group. Moreover, the annual revenues of single large corporations exceed the total sales of the entire SME industry many times over. This must be kept in mind while interpreting the results.

Although the Oulu region houses over 10% of the companies, more than Tampere, Kuopio, or Lahti, the number of employees in the region is comparatively low. This implies that the average company size is rather small, as illustrated in Table A2.1.

Given that Lahti is not considered a hotspot of Finnish biotechnology in terms of firm frequency, one might be surprised by the size of the region's workforce. The explanation is that Lahti is the home of a few old and well-established companies of considerable size.

Figure A2.2 displays the shares of total public R&D expenditures, industry R&D expenditures, and industry sales by region. The trend line could be interpreted in two ways. According to the first interpretation, one could say the figure displays a continuum, at the beginning of which is the amount of public money spent on basic research, with the second phase marked by industry-led R&D (fueled by

Figure A2.1 Spatial distribution of employment in the Finnish biotechnology industry, 2003-2004

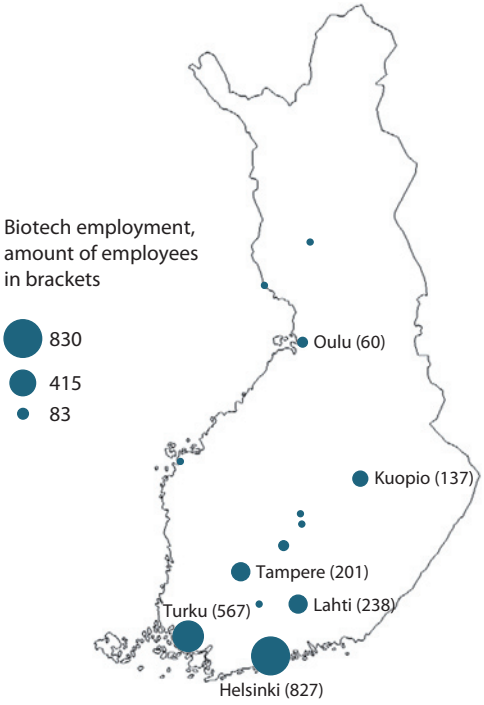


Figure A2.1 illustrates the employment distribution of the Finnish SME biotechnology industry. The Helsinki and Turku regions clearly boast the most labor, followed by the Lahti, Tampere, and Kuopio regions.

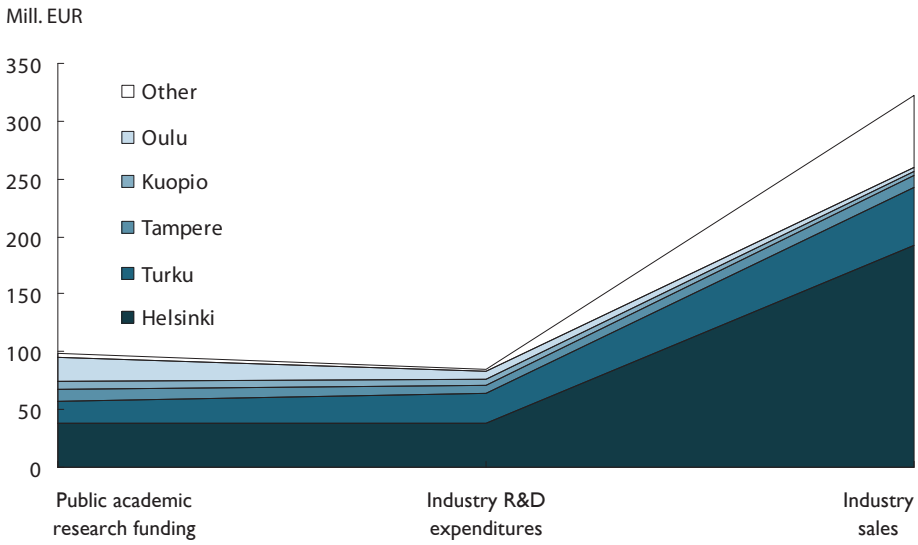
Source: Hermans and Tahvanainen, 2006.

Table A2.1 Average size of companies (number of employees) by region

Region	N	Mean	Minimum	Maximum
Helsinki	35	25	0	174
Turku	31	16	1	65
Tampere	6	34	3	75
Kuopio	7	11	1	30
Oulu	9	6	0	18
Other	9	43	2	238
All	97	22	0	238

Source: Hermans and Tahvanainen, 2006.

Figure A2.2 Comparison of academic research funding and industry input-output relation in biotechnology



Source: Hermans and Tahvanainen, 2006.

public money), resulting in commercialization in the last phase. Following this line of interpretation, the Helsinki region has done quite well in transforming publicly financed research first into successful private product development and then commercialization, by conquering close to 60% of markets reached by Finnish biotechnology companies. The relation between public–money-driven private R&D and the sales emerging from the R&D is always positive from phase to phase. Thus the Helsinki region seems to create value. In contrast, Turku also actively transforms publicly financed research into corporate R&D activities, but seems to perform less well in commercializing R&D with a share of about 16% of total sales in the industry. Kuopio and Tampere are similar to Turku, although they display much smaller volumes. Oulu seems to perform even more poorly, as the generous amount of public money flowing into the region does not lead to much R&D activity, which in turn is commercialized to an even lesser degree.

Another way of interpreting the figure is to look at it as a cross-section in time. One might say, for example, that the Helsinki region is already in a more mature state, having gone through all three stages and thus having set up the necessary down-stream assets and tapped into many markets. Following this interpretation,

Oulu might still be in an infant state of development, building up the infrastructure and company base necessary for successful R&D, to say nothing of commercialization. Given time, then, the region may very well create value. Thus, the figure might simply reflect regions in different stages of development, all growing towards the markets, as Helsinki already has.

However, these data fail to support the latter interpretation, as the average age of companies in the Oulu or any other given region does not deviate to a significant extent from the industry average. Thus, it seems that there are real differences in performance across regions when comparing the funding of the regional industries, the employment levels associated with the funding, and the regions' output.

Sales revenues provide, in addition to actual profits and a potential to pay dividends to owners, a vehicle for internal funding the company's R&D activity to generate further revenues later in the future. A company without sustainable revenues does not create value and is therefore unlikely to survive in the long run. Revenues and, of course, associated profitsstrengthen the balance sheet, making a company less dependent on outside financing often marked by stringent conditions and constraints hindering decision-making. Furthermore, internally generated equity is low-priced compared to externally supplied equity, because it entails no equity issue or administration costs. Again, the Helsinki and Turku regions account for the bulk of industry revenues, with Vaasa and the tiny southern town Hanko as runners-up. The revenue streams of the latter two regions benefit to a great extent from single well-established, mature companies well above the industry average in terms of sales. Tampere, Kuopio and Oulu remain far behind in aggregate revenues.

Helsinki

The Helsinki region is currently the biggest single hub of small- and medium-sized biotechnology companies, with close to 35% of the total. Especially strong in the fields of diagnostics and drug development, the region generated most (about 60%) of the revenues of the entire biotechnology SME industry in 2003, with close to 200 million euro. Bioinformatics, enzymes, and the agro-forest sectors are potential future growth sectors, as significant investments have already been made in terms of employment within them. The Helsinki region is also the most effective in converting public research money into corporate R&D and then into revenues, with total regional sales exceeding annual public sector investments and corporate R&D expenditures five-fold.

Turku

The Turku region is the second largest biotechnology hub in Finland, housing 32% of all biotechnology SMEs. It is the most versatile of regions, with active sectors including bioinformatics, drug development, diagnostics, environmental biotechnology, R&D services, enzymes, and especially food and feed. The sales of the Turku region constitute 16% of the annual total industry sales, with 51 million euro in 2003. Thus sector sales exceeded public research funding allocated to the region by close to 300%, and corporate R&D investments by almost 200%. It is interesting to note that the commercial performance of businesses corresponds to their relative ownership structures: Turku-based companies are primarily owned by government venture capitalists (VC), and to a lesser degree by private VCs.

Tampere

Tampere may be the most characteristic region of all. Although with just over 6% of all Finnish biotechnology SMEs and contributing just under 3% of total industry sales, the Tampere region focuses strongly on one sector: biomaterials. As such, the Tampere region is the only one to really specialize in just one sector. In terms of performance, the region is capable of generating turnover that exceeded annual corporate R&D investments by almost 60%, with 9.4 million euro in 2003. Still, public basic research funding dominates the figures (Figure B.2) with 10.7 million euro of public money allocated to the Tampere region for academic research.

Kuopio

Equivalent to Tampere in terms of the number of companies, Kuopio is another specialized region. Kuopio is a stronghold for both drug development and diagnostics, which is probably a manifestation of the decades-long local tradition of academic life science research. Based on regional public investments and corporate R&D expenditures, however, the performance of Kuopio-based companies is not very strong. Revenues in 2003 constituted just 55% of public funding and less than 90% of corporate investments in R&D.

Oulu

The Oulu region, third largest in terms of company frequency, may deserve special attention. One characteristic of note is that the region is rather diversified given its small size. Its focus is on R&D services, which is a solid base for generating basic revenue in the short run, but is not commonly regarded as a way of business with exponential growth potential, given that most returns on the developed products are reaped by the clients of these service companies. Thus, drug development, biomaterials and the agro-forest sectors are fields of application that might provide avenues of growth and future development in the region. However, such a broadly diversified strategy may be inappropriate for a peripheral region such as Oulu, as the poor sales output suggests. The region generates only 0.9% of total industry revenues, but receives over 20% of total public funding directed towards academic research in Finland.

Brezis and Krugman (1997) justify the existence of multiple peripheral centers by assuming that each of them specializes in the development of a technology with sufficient commercial potential, a technology based on knowledge distinct from that accumulated over time in older and more established centers. In other words, peripheral centers must specialize in the development of cutting-edge technologies, and, as such, always be a step ahead of the larger and established centers, rather than duplicating their efforts. These pre-conditions clearly set high demands on the innovative and commercial performance of companies in peripheral regions, and remind one that their justification for large government subsidies is far from self-evident.

If Duranton and Puga (2001) are to be believed, the more peripheral centers of the Finnish biotechnology industry would be well advised to maintain close relationships with the diversified centers of the Turku and Helsinki regions, in order to assimilate the knowledge those multi-disciplinary innovation hubs generate. Thus far, Helsinki is clearly in the position of a national collaboration hub. As Feldman and Audretsch (1999) conclude in an empirical study, larger diversified centers have a greater propensity to innovate than do specialized centers. In the spirit of Duranton and Puga (2001), the relocation of post-innovation activities from diversified centers to more specialized ones may reflect simple technology transfer, rather than physical relocation of activities. Thus the comprehensive R&D collaboration networks existing among the more peripheral centers and both Turku and Helsinki might be the expression of such transfers, speaking in favor of the interpretation above.

Diversified centers must first be aware of their multi-disciplinary nature, and its conduciveness to innovation. Building on the awareness, it is possible to coordi-

nate activities in a way that strengthens this effect and benefits local companies. If nurtured properly, these innovation-driving benefits will exceed the crowding-out effects of geographical agglomeration and ultimately justify the center's ongoing existence.

In contrast, it is paramount that more peripheral regions focus clearly on specific industry sectors. Only through specialization are these regions able to reap the benefits of intra-sector externalities, thus compensating for their failure to locate near more diversified centers, and reap the rewards of this location. In the case of biotechnology, the most central externalities are represented by knowledge transfers between local, often specialized academic centers and the industry, as well as among the companies themselves. Without these externalities, peripheral regions tend to gain no advantages over larger diversified centers and struggle to survive. Further, in light of this notion, a diversified strategy is not viable for a small peripheral region.

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Section II

Industry Conduct and Government Intervention: Policies and Results

CHAPTER 3

STIMULATION OF INNOVATIVE ACTIVITY IN DRUG DEVELOPMENT: INTENTIONS AND CONSEQUENCES

Morton Kamien[1]

3.1 Introduction

Transforming R&D into successful business ventures has remained an elusive task for most biopharmaceutical companies. The major obstacles lie within the "bio"-part, that is, the fact that biological systems pose challenges beyond the imagination of many business entrepreneurs. The very uncertain timetables stemming from this biological complexity and a comprehensive safety regulation challenge any financing arrangements based on IRR calculations or even public funding; the effective patent life can become too short for a viable business, discouraging new drug discovery (Figure 3.1).

This chapter deals with regulatory issues related to patenting and generic pharmaceutical competition in the world's largest health care market, the U.S. In this country the government sets IP regulations through specific laws in order to influence pricing and innovation in a desired direction. Recently, however, these regulations must also be in line with international agreements.

However, as indicated already in Chapters one and two, the government has a Janus' face: it tries to support innovativeness and new drug development, while at the same time exercising significant influence to reduce costs. Furthermore, public interest groups pressure the government to approve newer treatments more quickly.

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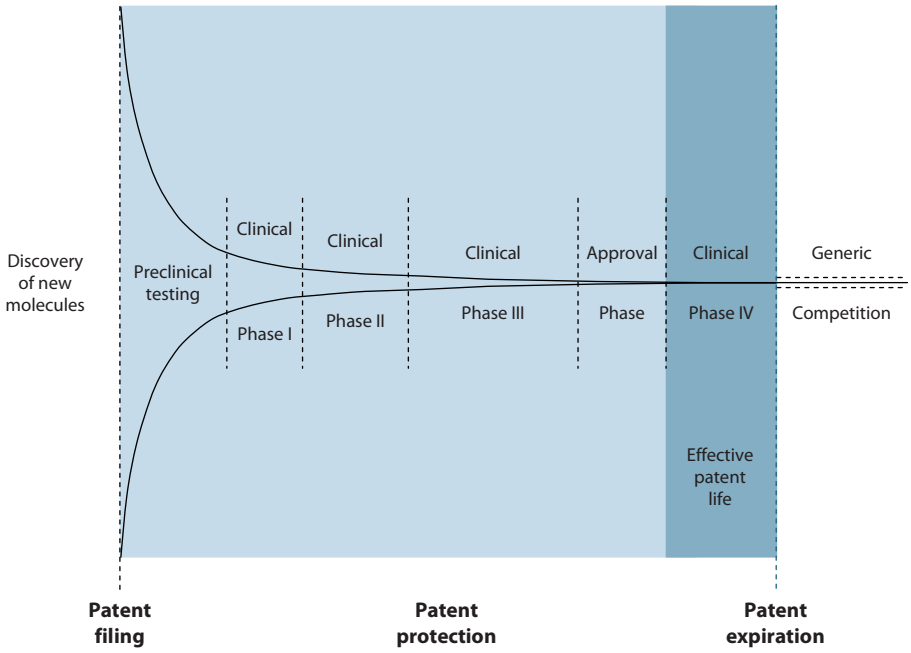
[1] Kellogg School of Management, Northwestern University, Evanston, IL.

Figure 3.1 Value chain of drug development: patent protection and generic competition



The public sector and the pharmaceutical companies are, therefore, engaged in a constant, delicate balancing act.

This chapter discusses the implications of three laws, The National Cooperative Act, The Drug Price Competition and Patent Restoration Act (Hatch-Waxman Act), and The Federal Fungicide Rodenticide Act (FIFRA), all of which were meant to stimulate innovation and foster competition. Further, the Hatch-Waxman act was intended to grant a prolonged monopoly and, thus, price advantage to original drug developers; this benefit is balanced by a price-reducing effect from enhanced generic competition after expiration of the patent life that the Act extends. Unfortunately, each of these laws has had unforeseen consequences that can frustrate their good intentions.

In addition, it is discussed how a single patent owner (monopolizing a specific part of the value chain) can form a gridlock for any further innovation by setting the out-licensing price too high. All this implies that the merger of all the individual monopolists into a single monopolist is Pareto superior. This seems to be Heller's

(2008) point as well with regard to a group of complementary patents. Even in the case of a single large pharmaceutical company.

The Drug Price Competition and Patent Restoration Act provisions are susceptible to manipulation by branded drug producers who introduce their own generic versions shortly before their patents expire. While this process might lower drug prices to consumers in the short run, it might also diminish the incentive to develop new and more efficient drugs that will benefit consumers even more in the long run.

The National Cooperative Act seeks to preserve price competition among joint research venture participants but not competition through innovation. It may be that a perfect incentive scheme for stimulating innovation does not exist, but awareness of the existing one's vulnerabilities can help antitrust authorities to anticipate and check problems.

The Federal Fungicide Rodenticide Act is susceptible to "me-too" registrants free riding on the incumbent manufacturers' costly registration efforts thereby discouraging innovation.

The discussion of competing interests will continue in Chapter 4, which analyzes comparative price regulation measures in the U.S. and Finland. The analysis yields somewhat surprising results as to how companies adapt to different regulatory environments.

3.2 Background

Demonstration that a perfectly competitive equilibrium is Pareto optimal, albeit under restrictive assumptions, is modern economic theory's affirmation of Adam Smith's claims for the virtues of competition. It is the virtues of lowest possible prices of a wide selection of goods and services that competition is alleged to bring that drive antitrust authorities to foster and preserve it. However, the fact that man has not yet succumbed to Malthus' subsistence steady state is a testimonial to the innovative ingenuity[2] that drives governments to foster technical advance through a variety of incentives including enacting intellectual property laws that create at least temporary monopolies or allow firms to cooperate in R&D activity. Unfortunately, there is a conflict between these objectives, because the perfectly competitive

[2] However Sir Martin Rees (2003) England's Astronomer Royal warns that the odds are no better than fifty-fifty that humankind will survive to the end of the twenty-first century.

market does not allow firms to realize extraordinary profits while technical advance demands it. It is commonly supposed that the prospect of extraordinary profits drives innovation while its rapid dissipation through price competition discourages it.[3]

The tension between price competition and innovation could be resolved if in fact both were regarded as operative in a modern economy. In other words, if changes in the production function were regarded as endogenously determined within the economy rather than exogenously, which is still commonly assumed in standard economics texts.[4] Schumpeter endogenized innovation in his "perennial gale of creative destruction"[5] that placed it above price competition as the primary form of competition.

> But in capitalist reality as distinguished from its textbook picture, it is not that kind of competition (price) which counts but the competition from the new commodity, the new technology, [...] competition which commands a decisive cost advantage or quality advantage and which strikes not at the margins of the profits and the outputs of existing firms but at their foundations and their very lives. [...] It is hardly necessary to point out that the competition of the kind we have in mind (innovation) acts not only when in being, but also when it is merely an ever-present threat. It disciplines before it attacks. The business man feels himself to be in a competitive situation even when he is alone in his field or if, not alone, he holds a position such that the investigating government experts fail to see any effective competition between him and any other firms in the same or a neighboring field and in consequence conclude that his talk, under examination, about his competitive sorrows is all make believe.[6]

As Andy Grove, an Intel founder put it, "Only paranoids survive." Schumpeter's Gale of Creative destruction has been witnessed, as entire industries have been blindsided by an innovation that wiped them out or threatened to. For example, the introduction of pocket calculators spelled the end of the slide rule industry, personnel computers made typewriters a thing of the past, and but for its marketing of the swatch watch, the digital watch would have consigned the venerable Swiss watch to history. Presently the digital camera has called the continued existence of

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[3] In fact Schumpeter (1934) who elevated the entrepreneur to the central role in getting science down to business, claimed that he was not motivated by the quest for profits but for other reasons. First of all, there is the dream and the will to found a private kingdom, usually, though not necessarily, also a dynasty. Then there is the will to conquer: the impulse to fight, to prove oneself superior to others, to succeed for the sake, not of the fruits of success, but of success itself. Finally, there is the joy of creating, of getting things done, or simply exercising one's energy and ingenuity.

[4] See Romer (1994) for an exposition of modern growth theories driven by endogenous technological advance.

[5] Schumpeter (1942), p. 84.

[6] Ibid. p. 84.

the film camera industry into question. And it appears globalization has reinforced the possibility of being blindsided by technological innovations from virtually any corner in the world.[7]

And while these events should drive incumbent firms to greater innovative activity it has instead sometimes turned them to finding creative ways of blocking entry. Thus instead of introducing new products or new methods of production to maintain their market position, that can arguably be claimed to benefit consumers, they have turned to introducing new schemes to block entry, thereby leading to the worst of both worlds.[8] For Schumpeter also recognized.

> Economic evolution or "progress" would differ substantially from the picture we are about to draw, if that form (Trustified Capitalism), of organizations prevailed throughout the economic organism. Giant concerns still have to react to each other 's innovations, of course, but they do so in other and less predictable ways than the firms that are drops in a competitive sea [...]. Even in the world of giant firms, new ones rise and others fall into the background. Innovations still emerge primarily with the "young" ones, and the "old" ones display, as a rule, symptoms of what is euphemistically called conservatism [...][9]

The open question for antitrust authorities is how to accentuate the positive and eliminate the negative? How to channel resources to create new products and services instead of new barriers to entry? This is an especially tricky issue because it is the very presence of the old established firms with their know-how and name recognition advantages that drives young firms, without fear of cannibalizing their existing businesses, to attempt to level the playing field by creating new technologies that give them the edge or at least an even chance.[10] This struggle between the young and the old is not confined to the business sector but can be seen in academia where it is the young scholars who often pioneer new theories or approaches.[11] The means by which old firms seek to maintain their dominance are often unexpected and require constant vigilance by the regulatory authorities.

This will be illustrated through three pieces of U.S legislation whose intended purpose is to stimulate innovation and further competition. The first deals with the

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7 Thomas L. Friedman (April 3, 2005).

8 Think Microsoft, U.S. Tobacco (see the US Appeals Court for the Sixth Circuit opinion in Conwood v. U.S. Tobacco) and 3M (see the US Appeals Court for the Third Circuit opinion in LePage's v. 3M).

9 Schumpeter (1939), p. 7.

10 Think Bill Gates, Paul Allen, Steve Jobs and Steve Wozniak.

11 Think Albert Einstein, Kurt Gödel, Werner Heisenberg, James Watson.

pharmaceutical industry in which the long time it takes for a drug to get Federal Drug Administration approval eats away a significant chunk of its patent life. The legislation seeks to remedy this situation by extending the drug's patent life beyond its original expiration date. The second deals with a similar regulatory lag problem in the pesticide industry in which obtaining a product's registration from the Environmental Protection Agency also eats away at its effective patent life. However, the remedy here is for its generic entrants to share the original developer's registration costs. The third deals with research joint ventures in which development costs are shared and R&D competition among the participants is eliminated.

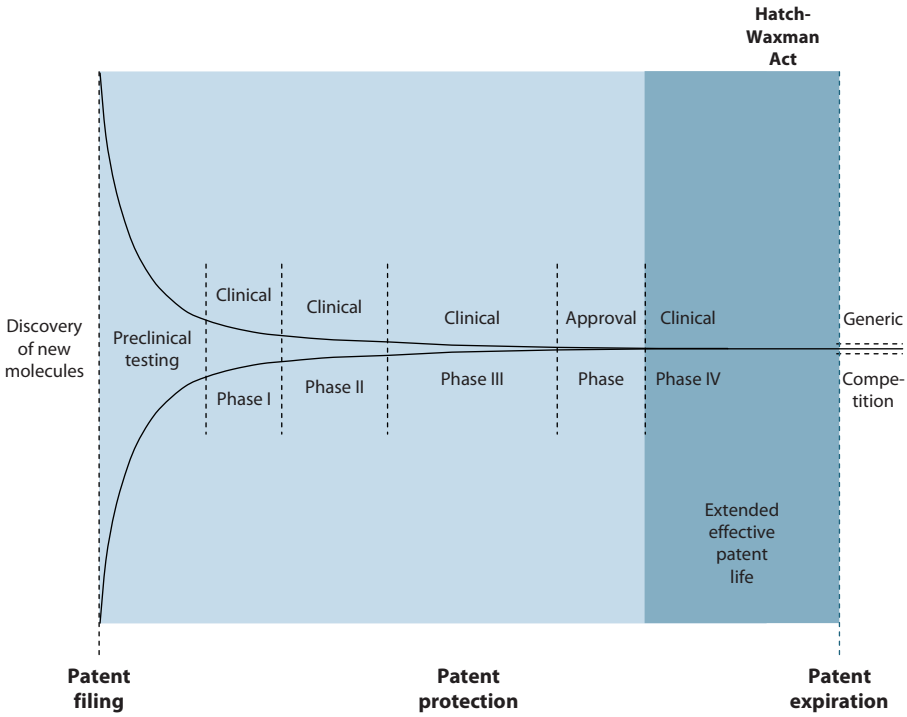
3.2 The Drug Price Competition and Patent Restoration Act (Hatch-Waxman Act)

The purpose of the Drug Price Competition and Patent Restoration Act, enacted by the United States Congress in 1984, was to offset the regulatory lag that patented drug developers experienced in getting their drugs to market which shortened the effective life of their then 17 year patent and thereby reduced their profits. The Act allowed for as much as five years of the patent being restored as long as the effective life of the patent did not exceed 12 years. Patent life restoration was in turn intended to maintain the incentive for new drug development which it was hoped would reduce societies,' including the government's, cost of providing health care (Figure 3.2).[12]

To offset the higher costs of the branded drugs that the Act's extension of the patent monopoly drove, the Act sought to accelerate the introduction of generic versions of branded drugs going off patent. This was done by requiring the generic producers to only show their version's chemical equivalence to the branded drug and to show that two hours after being administered its concentration in the bloodstream was within 20% above or below the concentration of the branded product. (The differences in the absorption rate of the generic versions of drug into the blood stream and the branded drug are driven by the differences in the binders used to make the pill.) Moreover, an eighteen-month exclusive marketing period is granted to the first supplier of the generic version. It was expected that

[12] According to DiMasi et al. (2003), the average out-of-pocket cost of bringing a new drug to market is $402 million and $897 million when fully capitalized including $92 million in post approval costs.

Figure 3.2 The Hatch-Waxman Act restoring patenting life of new drugs



the accelerated introduction of generics would drive intense price competition that lowered consumers' drug costs.[13]

However, some of the incumbent drug producers chose to introduce their own generic version of their branded drugs several months before they went off patent. While this strategy risks cannibalizing the incumbent firm's own branded product's sales it is better than having other generics producers cannibalizing them. And it enables the incumbent firm to take advantage of its unique ability to achieve the Stackelberg leader role in its patented drug's generic market by introducing its own generic version of it before its patent expires. Anyone else introducing their generic version of it has to wait until its patent expires in order to avoid risking

[13] The incumbent branded product producers have sometimes delayed registration of their generic versions by thirty months by claiming that they infringed on one of their unexpired patents on the drug.

patent infringement charges. Moreover it enables the incumbent to realize a higher profit that it would under its next best alternative of only being the Stackelberg leader in its branded drug and not producing its own generic version. That is, by only anticipating and taking into account the generic producer's optimal output decisions in determining its own optimal output decisions of its branded drug. Indeed, if some buyers regard the branded drug vastly superior to its generic versions the incumbent, who is also the Stackelberg leader in the generics market, can optimally raise its branded drug's price above the monopoly level it was charging before there was any generic entry. This is because while the higher price of its branded drug may drive some potential buyers to switch to a generic, its dominant share of the generics market makes it likely that the customer will buy its generic.[14] Thus, it is the combination of the higher price it realizes on its branded drug sales plus the dominant market share it realizes as the Stackelberg leader in the generics market, which is 50% in the case of a linear demand function and constant marginal cost that makes this strategy profitable. In fact, it would be profitable for the incumbent to introduce its own generic version of its branded drug even if there were no other generics, provided enough buyers regarded the branded drug as vastly superior. This would of course be difficult to do, although such cases do exist, as buyers would commonly assume that the two drugs are virtually identical. Ironically, the presence of a number of generic versions of the branded drug could help the branded drug to be regarded as vastly superior because of the variability of the absorption rates into the bloodstream among the competing generics. For example, long-term users of maintenance drugs who are especially sensitive to the variability in their absorption rates may be willing to pay the premium for the branded drug.

The upshot is that the profitability of introducing its own generic version of its branded drug shortly before it goes off patent may diminish the firm's incentive to innovate because of the extended profitability of its existing drug and increase its drug prices instead of spurring innovation and lowering drug prices as the Hatch-Waxman Act intended. The simple remedy would of course be to bar incumbent firms from introducing their own versions of their patented drug before its patent expires. This is because their generic introductions tend to be shortly before their branded drug goes off patent and so whatever cost reduction there is in the weighted average price of drug is brief.

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[14] See the appendix and Kamien and Zang (1999). See Scherer (1993) for an industry overview.

3.3 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

Since 1970 in order for pesticide manufacturers to obtain the required EPA approval to market them they have had to submit research data concerning their health, safety, and environmental effects. Conducting the required research and getting it approved is costly.[15]

Subsequent pesticide manufacturers who seek to market generic versions of pesticides going off patent also have to obtain EPA approval but can rely on the data previously submitted by their developers instead of conducting their own. However, these "follow-on" or "me-too" registrants have to offer to compensate the original data submitter.[16] If the "me-too" registrant's compensation offer is not acceptable to the original data submitter then the two have to submit to binding arbitration.

In the arbitration process the original data submitter commonly requests that the cost of the research it conducted be allocated on a per capita basis, because it provides each seller an equal opportunity to market the product while the "me-too" registrant requests that it be allocated on a market share basis to reflect its claims of a small market share. The original data submitter also requests that it be awarded a risk premium to reflect the risk it bore regarding the outcome of the research that the "me-too" registrant does not have to bear. The opportunity cost incurred by the original data submitter on the money devoted to securing the product's registration plus compensation for enabling the "me-too" registrant to market its product earlier than it would have had it done its own testing is also included in the original data submitter's claim.

The FIFRA remedy to the regulatory lag experienced in securing a product's registration focuses on sharing its full costs among the competing sellers of the product. Ideally it will lead to an economically efficient solution in the sense that only those "me-too" registrants who find it profitable after bearing their share of the full registration costs will enter the market. In other words, there will be no "me-too" registrants who entered because they received an implicit subsidy by not having to bear their share of the full registration costs and would not have entered

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[15] According to some estimates pesticide development costs are $60 million and take eight to ten years from discovery to registration. See http://www.ento.vt.edu/~mullins/pestus2004/notes/lecture/Lec25.html

[16] Fifteen years after the product's patent has expired the original research data leading toregistration becomes freely available to "me-too" registrants.

otherwise. Of course, if there are no entrants who find it profitable to enter the market without a subsidy despite the expiration of the product's patent then the original registrant does have to bear its full costs. But it is still better off than having to bear them when the product's price declines because of competition from rivals who did not bear their share of the costs. Finally, it is important to note that the FIFRA remedy deals solely with the costs of securing the product's registration and not with the product's research and development costs and the securing of its patent. It is by seeking to lighten the product developer's additional regulatory burden that FIFRA tries to maintain the incentive for firms to innovate such products rather than turn their innovation efforts to products that do not bear a regulatory burden. This is a real option for the pesticide producers who provide products to a variety of markets[17] in many of which the regulatory burden is small or non-existent.

On the other hand, the pharmaceutical companies[18] tend to focus their efforts on providing a variety of products to a single market in which they will all be subject to the same regulatory process. Thus, the Hatchman-Waxman Act focuses on maintaining their incentive to continue to develop new drugs by restoring the time they lose off the drug's patent life in the course of securing FDA approval. The government's interest in maintaining a flow of new drugs is driven by the fact that they tend to be a safer and less costly means of providing health care than the drugs and surgical procedures they replace. The entering generic version suppliers of drugs, which have gone off patent, are not required to share in their drug approval costs except indirectly by having to postpone their entry. Thus, the incumbent supplier of the patented drug is assumed to recoup its direct and indirect regulatory costs by having its patent's effective life partially restored. The economic efficiency of the Act is not immediately transparent.[19] A full-fledged comparison of the welfare effects in terms of price competition and incentives for innovation of the Hatch-Waxman Act's approach with the FIFRA approach would be interesting. Similarly, it would be interesting to know if incumbent pesticide producers have also implemented the strategy of introducing their own generic versions of their products before their patents expire in order to establish a Stackelberg leadership position in the generics market.

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17 Think DuPont, Monsanto, Union Carbide, DowElanco, and Syngenta among others.

18 For example think AstraZeneca, Bayer, Merck, Pfizer, and Wyeth.

19 Van Cayseele provides an insightful analysis of these issues.

3.4 The National Cooperative Research Act

The National Cooperative Research Act's enactment in 1984[20] was largely driven by the fear that Japan in particular and other countries in general were eroding the United States' leadership in developing high technology products by sponsoring cooperative research among competitors in their high technology industries.[21] The Act enables research joint ventures to register with the U.S. Department of Justice and to share information among their members that might otherwise be regarded as an antitrust violation, since information sharing among competitors often is so regarded. Moreover, if the research joint venture is sued in a criminal or civil action its behavior is judged on a rule of reason basis rather than as a per se violation of the antitrust laws and even if it is found guilty it is only subject to actual damages rather than treble damages.

In fact Japan did not displace the United States as the world leader in the high tech sector. Yet it is difficult to attribute this to the National Cooperative Research Act driving a steady growth in the number of new research joint venture filings in the United States from 1984 until 1995.[22] This is largely because measures of their effectiveness as gauged by the number or importance of patents generated, or their efficiency in generating patents or new products or processes appear not to be available. Link et al. (2002), taking into account that the number of research joint ventures (JVs) filings in the U.S. declined after 1995 finds that the propensity for American high tech firms to form research joint ventures to be inversely related to the intensity of foreign competition. Thus, he conjectures that as foreign competition eased off after 1995, U.S. firms' incentive to form JVs declined. However this conjecture may be at odds with the fact that a number of the research joint ventures formed during this period involved both U.S. firms and their foreign competitors.[23] The globalization of research joint venture membership plus the fact that the leading high tech firms conduct their research all over the world may

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[20] The Act was amended in 1993 to allow for production joint ventures in addition to research joint ventures.

[21] See Link et al. (2002).

[22] See Schacht (2003).

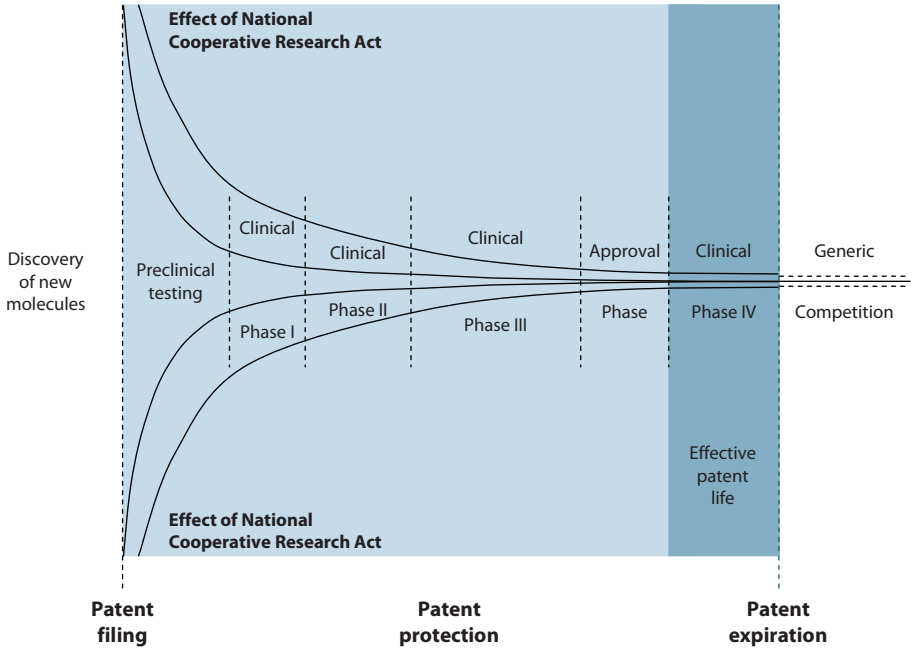
[23] The research joint ventures formed during this period included six competing research joint ventures composed of 18 firms seeking to develop cable boxes to deal with the increasing number of cable channels and three competing research joint venturescomposed of eight firms seeking to develop high definition television. A number of these research joint ventures included both American companies, Asian companies and European companies including Microsoft, Intel, Thomson Consumer Electronics, Phillips Electronics, Toshiba, and Matsushita among others. See Kamien and Zang (1993).

neutralize their role in driving any nation's technological leadership. Moreover, the primary drivers of the technological advances of the past fifty to sixty years, such as transistors, integrated circuits, personal computers, the Internet and the World Wide Web, laser technology, cell phones, the structure of DNA, and gene splicing, all came about through the efforts of individuals and independent enterprises not research joint ventures.

However, research joint ventures do provide a very appealing structure for conducting research, especially basic research for which there is no patent and which, therefore, becomes readily available to rivals. This, of course, discourages any firm from undertaking basic research and encourages it instead to wait to have a free ride on someone else's effort and to only undertake research that will not spillover to rivals. Research joint ventures have a number of additional advantages. First, the sharing of complementary expertise among the participants and avoidance of duplication of effort provides cost reductions. Second, spillover effects among rivals are internalized and costly efforts to prevent spillovers are avoided. Third, there is the indivisibility of a technical advance that makes it more profitable as its scope and magnitude of application expands. Fourth, the individual direct cost of a failed R&D effort is reduced compared to what it would be if the firm undertook it alone. All these advantages point to a single research joint venture comprised of all of the industry's participants as the most advantages (Figure 3.3). However, against all of these advantages of a research joint venture stands its great disadvantage of eliminating competition through innovation. The very type of innovation that Schumpeter regarded as the one "which strikes not at the margins of the profits and the outputs of existing firms, but at their foundations and their very lives." It is the kind of competition that drives rivals to innovate not only to grow but also to avoid being swept away by the rivals they know as well as the ones they do not know. Thus, the National Cooperative Research Act runs the risk of killing the very goose that lays the golden eggs it seeks to protect.

Of course, the absence of research joint venture performance data makes it difficult to formulate a cogent policy for antitrust regulators to follow to foster the production of the golden eggs. However, empirical studies may be drawn on that found that the most intense R&D activity occurs in markets where competition is intermediate between monopoly and perfect competition for guidance. A monopoly enables a firm to realize higher profits from its R&D investment than it can in the presence of competitors with the same technology and, therefore provides it with the highest incentive to innovate. Indeed, that is the rationale for patent monopolies and the patent restoration act discussed above. However, as Arrow (1962) states, a monopolist's incentive to innovate is dampened by having to deduct its current monopoly profits from the monopoly profits it will realize with its new technology

Figure 3.3 The National Cooperative Research Act



and the cost of developing it. On the other hand, a firm in an intensely competitive market typically cannot make profit from its invention to make its R&D investment worthwhile. But a moderately competitive market with competitors of comparable size provides each with enough opportunity to realize a substantial profit from innovating and the fear of losing profits to rivals by not innovating.[24]

If a single research joint venture composed of all the competitors in the market is the analog to a monopoly market in price competition, then the analog to a perfectly competitive market in prices is a market in which there are as many research joint ventures as competitors, that is one which each competitor conducts research independently. The analog to the intermediate market structure is a market in which there are a number of independent intermediate sized competing research joint ventures. It should then follow by analogy with the findings that markets with

[24] Kamien and Schwartz (1976).

intermediate levels of competition are the most research intensive, that a market with an intermediate number of competing research joint ventures should similarly be the most research intensive. This result can be demonstrated to be theoretically correct in the context of strategic competition among research joint ventures.[25]

In this model all of a particular research joint venture's members share their production costs reducing R&D results and coordinate their R&D spending strategically so as to maximize their venture's total profits from competition in differentiated products with the members of competing research joint ventures. They realize spillovers from the R&D efforts of the competing research joint ventures just as the competing research joint venture members realize spillovers from their R&D efforts. The competing research joint ventures are assumed to have an identical number of members. Thus as the total number of competing research joint ventures declines their memberships increase along with their product's sales and scope of application, both of which stimulate R&D investment. The increase in a competing research joint venture membership also makes it a more formidable rival by increasing its R&D spending capacity. This overall stimulus to R&D investment is proportional to the square of the number of members in each competing research joint venture, meaning that it grows nonlinearly. Thus, when each competing research joint venture's stimulus and scope of application are strong enough and the spillover effect among them is not too large then their combined R&D investment can exceed a single research joint venture's R&D investment. It also follows that when these conditions hold, having exactly two competing research joint ventures leads to the highest level of industry-wide R&D investment and the lowest possible product prices. This is because with a larger number of competing research joint ventures each venture's scope of application declines which diminishes its incentive to invest in R&D more than the increase in competition stimulates it. However, as the spillover effect grows, the incentive to have a free ride reduces the total R&D spending, which can only be overcome by the formation of a single research joint venture. These results apply as well to situations in which the competing research joint ventures are in different countries as long as there is international competition in the final products.

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[25] Kamien and Zang (1993).

3.5 Interdependence of patents

The IPR owner can be tempted to exploit the entire value of a venture despite its property being a crucial but small sub-section of the value chain (Venneste et al. 2006). This can lead to an under use of innovations and thereby forgone opportunities. In drug development, a single patent owner (monopolizing a specific part of the value chain) can form a gridlock for any further innovation by setting the out-licensing price too high. In order to prevent the creation of an 'anti-common', the whole society could gain from the creation of a patent pool. (Heller and Eisenberg, 1998; Heller, 2008).

Cournot (1838) presented a model for pricing the impacts of commodities (patents), the sole use of which is to be jointly utilized in the production of the composite commodity. He used brass production as an example in which the raw materials, copper and zinc, are jointly needed for the production of brass. The supply of copper is controlled by one monopolist, and the supply of zinc by another monopolist. Each sets the price independently to maximize its own profits. Therefore, the price of brass is higher than it would be if the supply of copper and zinc were controlled by a single monopolist. Moreover, if the number of components required to make brass grows, and the supply of each component is controlled by a different monopolist, the price of brass goes higher and higher, therefore, the demand for brass declines. In the limit as the number of independent components goes to infinity the price of brass increases to a point at which the demand for brass drops to zero.

All this implies that the merger of all the individual monopolists into a single monopolist is Pareto superior. This seems to be Heller's (2008) point as well with regard to a group of complementary patents.

3.6 Conclusion

The three acts discussed above were all meant to stimulate innovation and foster competition. Yet each has had unforeseen consequences that can frustrate these good intentions. The Drug Price Competition and Patent Restoration Act is susceptible to subversion by incumbent branded drug producers introducing their own generic versions shortly before their patents expire. And while this might lower drug prices to consumers in the short run it diminishes the incentive to develop new more efficient drugs that will benefit them even more in the long run. The Federal Fungicide Rodenticide Act is susceptible to "me-too" registrants free riding on the incumbent manufacturer's costly registration efforts and thereby discourag-

ing innovation. The National Cooperative Act seeks to preserve price competition among a research joint venture's participants not competition but through innovation. It may be that there is no perfect incentive scheme for stimulating innovation but awareness of the existing one's vulnerabilities can help antitrust authorities to anticipate them and check them.

APPENDIX 3

It is assumed that the respective inverse demand functions for the branded drug and its generic substitute are:

$$P_B = a - B - \chi G \qquad \text{(A3.1)}$$

$$P_G = a - B - G, \qquad \text{(A3.2)}$$

$\chi, 0 \le \chi \le 1$, is a measure of consumers perceived substitutability between them. If the prices of the two drugs are identical then consumers only purchase the branded drug. It is supposed that the n producers, $(n \ge 0)$, of the generic drug engage in Cournot competition among themselves, taking into account the presence of the branded product. The incumbent branded drug supplier maximizes its post patent expiration profits by acting as a Stackelberg leader with respect to the generics producers but does not produce its own generic version of its drug. It can be shown that the incumbent produces

$$B^* = \frac{a-c}{2}, \qquad \text{(A3.3)}$$

and charges

$$P_B^* = \frac{\left[n(1-\chi)+1\right]P^m + n\chi c}{n+1} \le P^m, \qquad \text{(A3.4)}$$

where $c \le a$, refers to the constant marginal cost of producing both the branded drug and its generic substitute and a refers to the choke price. The branded drug's price P_B^* is a convex combination of its monopoly price P^m and its perfectly competitive price c (when $n \to \infty$ and $\chi = 1$).

Total generic drug production is

$$G^* = \frac{nB^*}{n+1}, \qquad \text{(A3.5)}$$

and the generic drug's price is

$$P_G^* = P_B^* - \frac{n(1-\chi)\left(P^m - c\right)}{n+1}. \qquad \text{(A3.6)}$$

Thus, if the generic drug is perceived as a perfect substitute for the branded drug, $\chi = 1$, then their prices are equal and only the branded drug is sold. If $0 \leq \chi < 1$, then $P_G^* < P_B^*$ and $P_G^* \to c$ as $n \to \infty$.

On the other hand, if the incumbent produces its own generic version of its branded drug and assumes a Stackelberg leader role in the generic drugs market then it produces

$$B^{**} = \frac{(a-c)(2n+1)}{3+4n+\chi}, \tag{A3.7}$$

of its branded drug and charges

$$P_B^{**} = \frac{2a(1+n-\chi n)+c(2n+1)(1+\chi)}{3+4n+\chi}. \tag{A3.8}$$

Thus the incumbent reduces production of its branded drug relative to what it was producing when it was not in the generic drugs market. Moreover, if the incumbent is alone in the generics market, $n = 0$, then

$$P_B^{**} = (1-\chi)P^m + \chi c \leq P^m, \tag{A3.9}$$

as it is a convex combination of the choke price a, and the monopoly price. On the other hand when $n \to \infty$,

$$P_B^{**} = \frac{(1-\chi)a+2(1+\chi)P^m}{3+\chi} + \geq P^m \tag{A3.10}$$

Thus there is an n^* such that $P_B^* = P^m$ and for $n > n^*$, $P_B^* < P^m$. In other words, as the number of generic competitors increases the branded drug's price declines. However, with less than n^* rivals the branded drug's price rises after its patent expires. The intuition is that it is worthwhile for the incumbent to drive some consumers to buying the generic substitute when it has an overwhelming share of the generic market. Total generic drug production with the incumbent a Stackelberg leader in the generics market

$$G^{**} = B^{**}, \tag{A3.11}$$

That is, production of the generic drug exactly equals the branded drug's production. Total generic drug production exceeds its total when the incumbent is not in its market, since $G^{**} > G^*$.

The generic drug price is

$$P_G^{**} = \frac{2(1+\chi)P^m + (1+4n-\chi)c}{3+4n+\chi}. \quad \text{(A3.12)}$$

It approaches c as $n \to \infty$.

While production of the generic drug when the incumbent introduces its own generic version exceeds its sales when it does not, the sale of the brand drug declines. That is $B^{**} \leq B^*$, with equality occurring as $n \to \infty$. However, the total units sold of both the branded drug and its generic version when the incumbent also produces the generic drug exceeds its level when the incumbent does not produce the generic drug, that is, $B^{**} + G^{**} - \left(B^* + G^*\right) > 0$. Thus the average price of the drug must be lower when the incumbent is in the generic drug market than if it is not, especially as the number of generic drug producers increases, since they drive an increase in generic sales and a reduction in the branded drug's price. It is also more profitable for the incumbent to get into the generic drug market than not because its maximization problem would indicate that its sale of the generic drug should be zero, if it was less profitable. Of course, this relies on the assumption that consumers will not completely abandon the incumbent's branded product when it introduces its own generic version.

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CHAPTER 4

PRICE REGULATION AND INDUSTRY PERFORMANCE

Raine Hermans – Ismo Linnosmaa

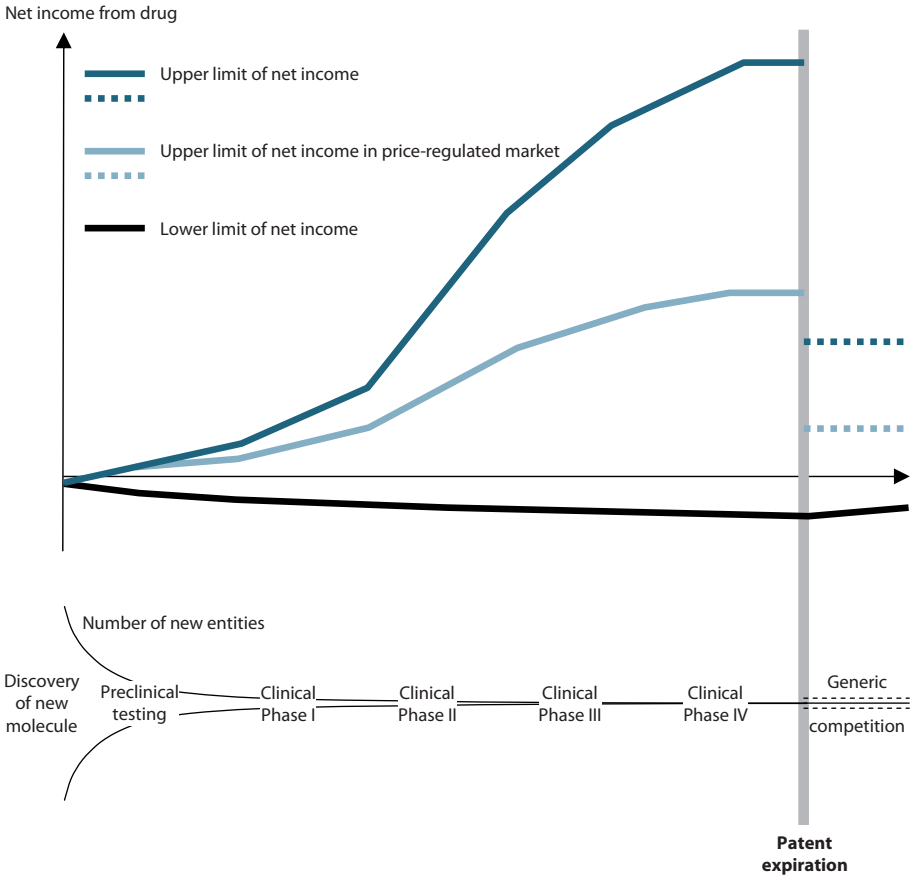
4.1 Introduction

This chapter provides information on how different price-regulation environments affect the price-cost margins of the pharmaceutical industry; or conversely, how pharmaceutical companies adapt to highly varying and changing regulatory environments. The approach is retrospective, with benchmark US data from 1970 to 1997, and Finnish data from 1975 to 1999. The Finnish data is particularly interesting as it covers two major legislative disruptions: the deregulation of drug prices, and the change from process patents (which aid the domestic drug industry) to the internationally required compound patent protection. For a further discussion we refer to Hermans and Linnosmaa (2007).

The US pharmaceutical industries price markups, or price-cost margins, are compared to Finland's highly regulated governmental price-setting system. Theoretically, the estimation rests on a modification of the conventional growth model and its extensions for imperfectly competitive markets. The results show that the price markup estimates are relatively close to each other and differences in regulatory environments have not altered the price markups in the pharmaceutical industry in these two countries.

Both the literature and the previous chapter indicate that prescription drug prices react to governmental interventions. While legislation influences *prescription* drug prices, there is an opposite variation in the price of over-the-counter (OTC) medications. This finding indicates that in all but completely regulated markets, the drug companies' pricing strategies across countries yield a similar overall profitability. From a legislative point of view, the results imply difficulties in setting up and sustaining an effective price regulation system.

Figure 4.1 Net income from drug development in distinct phases



4.2 Background

The pharmaceutical markets and drug development are highly regulated by governments. The government regulation of patient testing and drug approval aims at reducing the risk for development of unnecessary or harmful pharmaceuticals. In addition to that, prices of pharmaceuticals are regulated in many countries to reduce the pressure for persistent increases in health care costs.

The aim of this chapter is to provide information on how different regulative environments affect the price-cost margins and present value of the pharmaceutical industry. To that end, we assess the historic price-cost margins of the pharmaceutical industry of two countries, Finland and the USA.

Before joining the EU, Finland was able to subsidize the domestic pharmaceutical industry by patent regulation by approving process patents: if one was able to generate the drug molecule, approved by any other country, by other than the original process, the process patent could be filed and the patent protected drug produced in Finland for the domestic market. The impacts on industry profitability will be investigated in this section below.

After Finland joined the EU, the patenting procedures have been harmonized and the Finnish pharmaceutical markets meet the global competition. The simulation is based on this and R&D expenditure projections have been obtained from the expenditure distributions of companies' international counterparts. Although the traditional advantage of the Finnish pharmaceutical industry has been based on the cost competitiveness because generated by the plausible regulation of intellectual property rights, the future seems different: the industry is challenged by the harsh competition in the global markets.

The argument here is that the sustainable competitive advantage should be based on highly differentiated technologies able to generate cost reductions for the health care payers. Accordingly, instead of low R&D expenditures, the most effective strategy could be based on the highest health impacts for the patients and thus the highest potential long-run savings for the payers. The strategy would drive up the price markups of the pharmaceutical industry as well.

4.2.1 Historic view: price markups in Finland and the USA

The Finnish pharmaceutical market has been controlled by a strict governmental price regulation system, whereas the pricing in the US market has relied on the market mechanism. The pharmaceutical industry in both countries seemed to rely on their domestic markets as their main geographic target during the period under investigation: the Finnish and the US pharmaceutical industries exported on average 20% and 8% of their total output, respectively. Finland's market orientation clearly is, however, towards international markets: the export share rose from 5% to 30% over time; but the US export share varied around the average.

The stringent price regulation of the Finnish pharmaceutical market has experienced some changes (see e.g. Rinta, 2001). Before 1995, the approval of a pharmaceutical product for the public reimbursement system was linked with the

institutionally-set price. Since 1995, drug prices have been deregulated in principle. However, if the company applies to accept the drug as part of the Finnish reimbursement system, the pharmaceuticals pricing board sets the price at twice the amount refunded.

The size of the US market is 200 times larger than that of Finland. On the one hand, the large size of the markets could theoretically imply some closeness to the features of perfect competition. On the other, because there are many patent protected products with some monopoly power, one would expect that many US companies, without direct price regulation, would charge more than their counterparts in a more regulated setting.

4.2.2 Methods and literature

The method in this study is based on Solow's (1957) seminal work. The estimation procedure consists of Solow's method for measuring technical change called Solow's residual. The model ignores the question of increasing returns to scale by assuming constant returns to scale in production. Hall (1988) and Domowitz et al. (1988) developed the model and analyzed Solow's residual in both perfect and imperfect competition frameworks. They showed that Solow's residual is independent of the growth rate of the output-capital ratio if perfect competition prevails. However, if the market is imperfectly competitive, there is a correlation between the two variables and the growth of the total factor productivity is pro-cyclical.

The estimation of price-cost margin can be based on the Solow's residual setting. The method was applied by Linnosmaa et al. (2004). They estimated the price-cost margin of the Finnish pharmaceutical industry. The estimation employed time series data and provided a fixed price cost margin over time. The present paper extends that application and utilizes R&D expenditures and estimated R&D stock in order to take R&D stock into account as a productive input in the pharmaceutical industry both in theoretical and empirical settings. This modification is justified given the high R&D intensity of the pharmaceutical industry. In order to compare the price-cost margins in the markets with different price regulation environments, the empirical setting employs not only Finnish but also US data.

There is a great need for international price comparisons of pharmaceuticals particularly those being utilized in regulatory planning activities. The price comparison studies provide important information on international price levels of pharmaceuticals (e.g. Danzon and Chao, 2000; Berndt et al., 1995). Such information is conventionally combined with information on the costs of pharmaceutical production and research and development (R&D) and then utilized in decision-

making and regulatory planning. However, there seems to be a lack of indispensable information on factors affecting price levels.

The price comparison studies clearly describe the situation, but do not explain why price levels differ. Factors behind the price differences can be derived from the cost structures of firms, regulatory practices, or domestic income levels, and degree of competition. In order to take into account the three former factors, this article measures the price-cost margins. These estimates directly take into account the cost structure of the pharmaceutical industry, and indirectly most of the other above aspects.

The impacts of the different regulatory practices are analyzed by comparing the Finnish and US pharmaceutical industries. The Finnish industry sells mainly to their highly price-regulated domestic market. The US sells to their domestic market, which relies heavily on market mechanisms for price setting. The domestic income levels of both countries are used as an instrument in the empirical model. The impacts of market structure and degree of competition are discussed while interpreting the empirical results in Section 4.

Alternative and quite appealing approaches to estimate price-cost margins can be found in Berry et al. (1995), Feenstra and Levinsohn (1995), and Bresnahan (1987). These articles construct explicit economic models on the consumer, producer, and market behavior and utilize product-level data to make inferences on economic variables present in economic models. The method used in this article requires no specific structure on consumer preferences, because making assumptions about consumer preferences would be too restrictive in the case of aggregate data, which aggregates the consumption of all pharmaceuticals on the market. In some cases aggregation of preferences is certainly possible (see Gorman, 1959), but not in general. These observations support the use of the current method.

4.3 Empirical analysis for historic assessment

4.3.1 Data

The sample is restricted to two countries because there was no further international data available which was plausible for measuring price-cost margins. However, the data provides a good fit for the reason argued above in Section 1: Finnish pharmaceutical markets have been highly price-regulated compared to US markets. Thus, price-cost margins in markets can be compared with respect to price regulation, and provide new information on the effects of the price regulation.

The data on the US pharmaceutical industry was collected from the OECD Health data and OECD STAN database. R&D figures for both countries were taken from the OECD ANBERD database. The data set for Finland was aggregated from the firm-level data in Statistics Finland. It contains all Finnish pharmaceutical firms with more than 20 employees. The firm-size restriction was made in order to avoid the problem of inconsistent data in the capital stock variable. The capital stock figures for the smallest firms were deemed to be unreliable over time. Figures on pharmaceutical expenditures were obtained from OECD Health Data.

The US data set covers the time from 1970-1997 and the Finnish data from1975-1999. The R&D information covers 1973-1997. The data set contains information on nominal and real output, nominal and real value added, working hours, the number of employees, labor costs, R&D investment, and capital stock. The capital stock series was constructed from data on capital stock per labor hours. Table 1 below presents the descriptive statistics of the growth rates of the original variables used in this study. Output, value added, wages, and capital stock variables are measured in Finnish Markkas (FIM) and in US dollars (USD).

Table 4.1 presents the real growth rates of value added, labor, capital, R&D expenditures, estimated R&D stock, GDP, and nominal pharmaceutical expenditure.

Volume indices for output and value added were constructed in Statistics Finland and are presented in 1995 prices for the Finnish data. Excluding the instrument variables, ready-made data in both value and volume terms was recieved. The nominal expenditure on pharmaceuticals and gross domestic income were used as instruments (regressed towards output-capital ratio in the first stage of the models). Data for the first instrument were obtained from the Social Insurance Institution of Finland while all the other data came from Statistics Finland. The volume indices for R&D data were constructed utilizing the GDP price indices. In the US data, the volume of production was estimated utilizing pharmaceutical prices that were used as a production price deflator. The capital stock volume was formed employing the price index for investments in the US chemical industry.

The first two instruments employed in models 1 and 2 – the growth rate of the nominal expenditure on pharmaceutical products and the growth rate of real GDP – can be held as indicators which are demand-driven and do not affect the total factor productivity. Instead, a third instrument, the growth rate of real R&D expenditures with a lag of one year, is more problematic. If most of the R&D activities concentrate on improving the production processes of pharmaceutical firms, they boost the productivity. In this case, the instrument is not valid due to the causal relation with the dependent variable. But, if the R&D activities were mainly channeled to long-term drug development, they would not be closely mirrored in the short-term

Table 4.1 Descriptive statistics, percentage annual rates of growth in volumes (1995 prices)

	Average, %	Std. deviation, %	Minimum, %	Maximum, %
Value added				
USA	4.6	5.2	-4.7	18.4
Finland	6.2	19.6	-14.9	82.9
Labor				
USA	2.7	3.0	-3.4	8.6
Finland (working hours)	1.9	5.4	-6.9	10.4
Capital stock				
USA	3.1	6.8	-11.4	14.6
Finland	7.6	15.1	-21.1	41.6
R&D expenditure				
USA	7.4	5.8	-6.2	19.4
Finland	6.9	7.9	-12.7	24.9
Estimated R&D stock				
USA	7.5	1.3	4.6	9.7
Finland	7.4	2.7	3.2	13.8
Domestic pharmaceutical expenditure (in current prices)				
USA	9.7	2.0	5.8	13.6
Finland	11.0	4.1	5.3	21.8
GDP				
USA	3.1	2.3	-2.1	7.3
Finland	2.2	3.1	-6.3	6.8

Source: OECD Health data, OECD STAN database, OECD ANBERG database and Statistics Finland.

fluctuations in productivity. Keeping this in mind, the lag growth rate of real R&D expenditure was added to one of the models as an instrument.

4.3.2 Variable construction

The variables are straightforwardly constructed on the formal model above. First, variables are converted from nominal to real terms. Then the annual changes are measured and contrasted with the growth rate of the capital stock (equation 8). The new and most critical part in the variable construction is the formulation of the R&D stock as part of the price-cost margin estimation procedure.

The R&D stock is applied in this study, instead of employing R&D expenditures, because the theoretical model employs the growth of stocks. The development in the growth of stocks is smoother over time than the growth of expenditure. The concept of knowledge stock is comparable to the capital stock presented in the original model. Second, R&D efforts seem to affect the knowledge stocks with lags. The stock changes after a lag compared with R&D expenses.

About half the R&D expenditure is wages (Guellec and Ioannidis, 1997). Part of the R&D costs is intermediate input and capital investment. Accordingly, half of the R&D expenditure is deducted from the total cost of labor compensation to avoid counting it twice. Part of the R&D-related investment in equipment is possibly also documented in the capital stock, which may lead to counting the same data twice. Unfortunately, the data on intermediate input and share of R&D-related capital stock were not available. If R&D stock and capital stock are counted twice, the Lerner index in the empirical model could even be negative. When these inputs are not reduced from the estimated figures, this has two possible impacts. It can distort the growth rates of R&D stock and the share of R&D stock of the total value added. The first mentioned effect is restricted if the input changes symmetrically with the growth of the entire stock. However, the share of R&D stock can be overestimated, which in turn causes the Lerner index to be underestimated. However, when the data of both countries are treated similarly, the comparison is expected and uniformly reflects the reality. It is also illustrative to compare the results of both models, with and without the R&D stock effect.

The R&D stock is created as follows. First, the R&D stock is calculated by conventional accounting standards and is formed by multiplying the R&D expenditure of the first period, 1973, by a factor of five. Five years is a conventional and cautious estimate for the range of the economic influence of the expenditure on R&D activities in conventional accounting standards. That is, the research and development activities this year are expected to affect the earning prospects of the industry during the next five years on average.

The ratio between R&D investments and R&D stock is approximately 1/5. In other words, the actual R&D expenditure is assumed to be the best estimator for the cumulative R&D stock. In order to fill this condition, the annual depreciation rates of R&D stocks in both countries were fixed. The fixed depreciation rate of real R&D stock for Finland is estimated at 14.5% and the US at 14.0%. The GDP deflator has been employed as a proxy for R&D prices. Hence, the real R&D stock grows as much as the real annual R&D expenditure and is depreciated by the fixed rate above. This corresponds to a 7.4% real rate of growth for the R&D stock in Finland and 7.5% in the US. In this setting, the cumulative nature of knowledge, which is applied and formed in R&D activities, can be utilized.

4.3.3 Empirical model and results

The empirical estimation is based on a formal model presented in Appendix 4 in the end of this chapter. A linear regression model is estimated as follows:

$$r_t = \alpha_1 + \alpha_2 q_t + u_t \ . \tag{4.1}$$

The left-hand side equals Solow's residual r_t and the independent variable corresponds to the output-capital ratio in the right-hand side of equation A4.8 in the Appendix 4. The independent variable is endogenous because the output-capital ratio appears on both sides of equation 8. The 2SLS estimation technique is used to estimate the above model.

First, the model is estimated without the R&D stock variable and then later this variable is added to the model. The nominal growth of pharmaceutical expenditure and the real growth of the GDP are utilized as instruments in two regression models estimated using 2SLS techniques. Table 4.2 presents the estimation results of model 9 for both instrument variables. The estimates of the pooled regression model are also shown.

The results propose that Solow's residual is strongly pro-cyclical both in the US and Finnish pharmaceutical industries. The correlation between Solow's residual without R&D stock and the growth rate of the output-capital ratio is 0.978 ($p < .01$) in Finland and 0.919 in the US ($p < .01$). The correlation between value added and factor productivity is 0.962 ($p < .01$) in Finland and 0.880 ($p < .01$) in the US. All of the correlation estimates deviate significantly from zero. This implies the simultaneous determination of Solow's residual and the output-capital ratio. In other words, changes in both variables are pro-cyclical.

Table 4.2 presents the estimates of the Lerner index when Solow's residual does not include the growth of the R&D stock. Estimates for the price-cost margin in the Finnish pharmaceutical industry range between 0.597-0.668 and in the US between 0.512-0.671. According to the t-tests, any pair of Lerner indices, obtained by different instruments, does not differ from any other between Finland and the US ($p < .05$). The estimates for the Lerner indices in the US pharmaceutical industry are close to those obtained by Scherer and Ross (1990). The results obtained from the Finnish pharmaceutical industry in the first model setting without R&D stock are equivalent to those of Linnosmaa, Hermans, and Hallinen (2004). However, this empirical setting contributes to Linnosmaa et al. (*ibid.*) study in two respects. First, this study analyzes the impact of R&D inputs separately. Second, the same method is applied regarding the US data.

Table 4.3 presents the results of the model, which contains the R&D stock in Solow's residual. The change in the R&D stock-capital ratio is now weighted by R&D expenditure per value added (R&D share) according to equation 8. Half the R&D share estimates are labor wages, which are, in turn, deducted from the total wages. The price-cost margins vary between 0.43-0.55 in Finland and 0.40-0.58 in the US. According to the t-tests, the Lerner indices do not differ significantly ($p < .05$) between Finland and the US. Despite some contradictions between the results

Table 4.2 Results of Solow's residual 2SLS model with labor and capital inputs

Dependent: Solow's residual	R^2 (adjusted R^2)	Constant (α_1)	Lerner index (α_2)
Instrument: growth of GDP/capital			
USA	.8010	.0077	.5120***
	(.7927)	(.0060)	(.0847)
Finland	.8564	.0193	.5970***
	(.8499)	(.0162)	(.1437)
Pooled data			
Fixed effects	.8405	.0127	.5766***
	(within groups)	(.0085)	(.0926)
Instrument: growth of pharmaceutical expenditure/capital			
USA	.8060	.0076	.5207***
	(.7979)	(.0059)	(.0868)
Finland	.9001	.0200	.6683***
	(.8956)	(.0135)	(.0985)
Pooled data			
Fixed effects	.8792	.0126*	.6382***
	(within groups)	(.0074)	(.0697)
Instrument: growth of lagged R&D expenditures/capital			
USA	.8523	.0094*	.6709***
	(.8449)	(.0047)	(.1044)
Finland	.8663	.0194	.6114**
	(.8602)	(.0157)	(.1588)
Pooled data			
Fixed effects	.8710	.0145*	.6212***
	(within groups)	(.0082)	(.1058)

Method: 2SLS and on pooled data 2SLS fixed effect model.
Standard errors are in parentheses. The asterisk labels stand for statistical significance of:
* 10 percent, ** 1 percent, *** 0.1 percent.

of the models, the results of the R&D stock-corrected models clearly show that the mark-ups are lower than the estimates from models that do not take into account R&D effects. However, the t-tests show that the Lerner index decreases significantly only in Finland when pharmaceutical expenditure is used as an instrument and the R&D stock effect is taken into account.

The results of model 1 state that the estimated Lerner indices differ significantly from zero and they are 0.44 in Finland and 0.40 in the US. This implies the approximated price-cost ratios are 1.79 and 1.66, respectively. Instead, the constant term does not deviate significantly from zero. The constant term partially describes the effect of technical change without the estimation of the growth of R&D stock (see equation A4.11 in Appendix 4). When the growth of the R&D stock is added to the model, the R&D effects can be expected to capture much of the effect of technical change. Due to the inclusion of the R&D stock in the model, it seems logical that the constant term does not differ significantly from zero.

Model 2 estimates the values of the Lerner indices to be 0.55 in Finland and 0.44 in the US. Hence, the price-cost ratios are higher than in model 1 in both countries, 2.25 in Finland and 1.77 in the US. Models 1 and 2 imply that price-costs margins are higher in Finland than in the US. However, model 3 alters the comparative ranks of the countries. The Lerner index of the Finnish pharmaceutical industry is 0.43, which equals the value of the price-cost margin of 1.75. The Lerner index of the US pharmaceutical industry is 0.58 and the price-cost margin is correspondingly 2.39.

In one case (Table 4.3, model 3, Finland), the Lerner index does not deviate significantly from zero. The correction of heteroscedasticity by White's robustness check altered the standard error and significance of the coefficient so that the Lerner's index became significant in this model ($p < .05$).

4.4 Interpretation of results

There can be two potential reasons for the similarity of price-cost margins in the pharmaceutical industry in Finland and the US. If the markets are otherwise identical in Finland and the US, but price regulation is applied in Finland, then the price regulation is not binding. In this case, Finnish authorities could either scrap the entire regulatory system or alternatively tighten price regulation. The first alternative could be optimal in the case of a costly regulatory system.

The other explanation for the result is that the markets are not otherwise identical (see *e.g.* Joskow and Rose, 1988). Market structure, technological advancement,

or governmental interventions could be very different in the two countries. In this case, the price regulation may be binding. There are even other forms of regulation that affect the market structure and prices to some degree. For instance, the US administration tightened the regulation on the safety and efficacy of prescription drugs during the 1970s. If the Finnish drug approval system has not been as stringent as its American counterpart, this might have implied a potential for the Finnish pharmaceutical companies to gain higher price markups.

Table 4.3 Results of Solow's residual model with labor, capital, and R&D inputs

Dependent: Solow's residual (rt)	R^2 (adjusted R^2)	Constant (α_1)	Lerner index (α_2)
Model 1: growth of GDP/capital as an instrument			
USA	.6815	-.0029	.3963**
	(.6671)	(.0063)	(.1133)
Finland	.7125	.0073	.4424*
	(.6988)	(.0234)	(.2097)
Pooled data			
Fixed effects	.6032	.0007	.3878*
	(within groups)	(.0136)	(.1530)
Model 2: growth of pharmaceutical expenditure/capital as an instrument			
USA	.7130	-.0029	.4355***
	(.7000)	(.0060)	(.1014)
Finland	.8138	.0093	.5549**
	(.8049)	(.0187)	(.1361)
Pooled data			
Fixed effects	.7067	.0015	.5091***
	(within groups)	(.0117)	(.1108)
Model 3: growth of lagged R&D expenditures/capital as an instrument			
USA	.8336	.0005	.5823***
	(.8253)	(.0048)	(.1055)
Finland	.6979	.0071	.4287
	(.6836)	(.0240)	(.2496)
Pooled data			
Fixed effects	.6213	.0027	.3983*
	(within groups)	(.0145)	(.1947)

Method: 2SLS and on pooled data 2SLS fixed effect model.
Standard errors are in parentheses. The asterisk labels stand for statistical significance of:
* 10 percent, ** 1 percent, *** 0.1 percent.

There seem to be some other differences between the regulations affecting the market structure of these two countries. For instance, Finland used to allow process patenting: Finnish companies have been able to produce the drug molecule (already patented abroad) if they developed and patented a production process different from the original one. Therefore, the Finnish pharmaceutical industry had a regulatory advantage in generating [copying] patent-protected products to the domestic market by comparatively low R&D expenditures. However, after the harmonization of their patenting legislation with the EU legislation in 1995, the Finnish companies met the same challenges as their foreign counterparts, putting pressure on their price-cost margins.

The differences in the regulatory measures and size of the markets of Finland and the USA could raise some questions on the assumptions behind the analysis. While the theoretical model assumed constant returns to scale in the production function, it should be borne in mind that there would be a difference in the price-cost margin in the two countries due to the economies of scale in production in two perspectives. First, if the industry could achieve increasing returns to scale in its production processes, the average costs of production would decrease with higher volumes of production. However, marginal costs do not necessarily decrease together with the decrease in average costs if, for instance, the cost function is linear. Second, if marginal costs also decrease along with production volume, then higher price-cost margins could be expected in the US than in Finland, and vice versa, if there are increasing marginal costs. Third, there could also be a certain point or points in production volumes at which the marginal costs begin to decrease or increase in a given time. This can be, for instance, due to additional costs of hiring new employees from other sectors. For these reasons, it would be of great importance to investigate the scale economies in further research.

Before 1994, price setting was linked to the market authorization of the pharmaceutical product in Finland (Rinta, 2001). Price regulation used to be tied to the reimbursement system and aimed at defining the reasonable wholesale and retail price of pharmaceuticals. If a company wanted to include its product in the reimbursement system, Finnish authorities set a maximum price level for the product. In contrast, prices are set by the market in the US system.

The US markets are divided into two parts. First, there are drugs that are patent protected and, second, there are generic drugs without patent protection or the patent has expired. The large marketplace implies higher potential returns in the first case with high market power. The second case of generic competition implies that there might be almost perfect competition due to the large number of suppliers and consumers. In Finland, the market was relatively closed. The Finnish companies produced many compounds under license, as well as their own brands.

There has also been a tradition of branding even non-prescribed generic domestically produced pharmaceuticals for Finnish markets. In other words, there is some kind of market dichotomy in both countries.

The nature of the markets can be a partial explanation for the similar price-cost margins. In other words, high mark-ups obtained from patent-protected products can be offset by low margins within severe generic competition in the US. In Finland, regulated prices of prescribed products may imply relatively low mark-ups, which were offset by relatively high mark-ups of non-prescribed branded products in generic markets.

4.5 Conclusion

The above information on how differences in price-regulation environment affect the price-cost margins of the pharmaceutical industry has been provided. price-cost margins in the pharmaceutical industry of the US, with large and competitive markets, and Finland, with tightly regulated markets have been compared. The study applied a uniform estimation technique, based on the application of imperfect competition of the conventional growth theory. Solow's residual for the both countries was estimated in order to get comparable results in the markets in which price regulation systems are different. According to the results, price-cost margins do not differ between Finland and the US.

The model analyzed the effects of changes in R&D expenditure. This allowed the impact of specific features of R&D intensity in the pharmaceutical industry on its price-cost margin to be assessed. The price-cost margin seemed to decrease by less than 10 percentage points in the US when R&D stock is included in the model. However, the absolute effect was above 10 percentage points in Finland. The difference is statistically significant only in Finland, as pharmaceutical expenditure is employed as an instrument. The notion is, in that part, in accordance with the theory. It also shows that conventionally estimated price-cost margins can be generally higher without implementing the impact of R&D expenditure on the measures. This particularly holds true in R&D-intensive industries, such as the pharmaceutical industry.

The results raise some questions about the efficiency of regulatory settings and the differences between the market structures. If the market structure is the same in both countries, then price regulation is not binding in Finland, and either the regulation should be tightened or eliminated. If there are also differences in market structure and the competitive environment, as seems to be the case, the

policy implication above is no longer so straightforward. If, for instance, the branded US pharmaceuticals are more expensive and the US fiercely competitive generics cheaper than their Finnish counterparts, this might lead to the same margins on average. This would lead non-US producers of branded drugs to seek profits in the US markets. The same logic suggests that some US generic producers could generate abnormal revenues from highly regulated markets.

There is a need for further research covered at least in some parts below. First, it would be important to test the impacts of policy changes on the firms' price-cost margins over time. The next section conducts a simulation of how the earnings prospects of the Finnish drug development changes will change under the internationally harmonized Finnish patenting system. A more careful investigation of the market structure and the significance of foreign trade should be considered in further research. Chapter 3 already discussed how regulatory acts regarding prices and market conditions affect the corporate strategies in the US pharmaceutical markets. Since the drug development takes a relatively long time before the market launch, the value of the projects varies significantly over time. The next chapter simulates the capitalized value in distinctive development phases.

Appendix 4

Theoretical model for the price-cost margin estimations

The model is applied from Hall (1988); Domowitz et al. (1988); and Linnosmaa et al. (2004). Adding research and development (R&D) input as a distinct factor of production in the model contributes to the theory, because R&D input can be held as a particularly critical factor in developing new products in the pharmaceutical industry. Thus, the production function is the form:

$$Q_i(t) = A_i(t) f_i\left(L_i(t), S_i(t), K_i(t)\right) \tag{A4.1}$$

where *i* is the country-index referring to either the USA or Finland, *Q* signifies production, *A* is a measure for the technical change not captured by other factors of production, *L*, *S*, and *K* denote labor, research and development, and capital inputs, respectively. The term *t* stands for time, implying that all the variables are measured at a certain time. The above modeling approach allows production technology, technical progress, and the use of inputs to differ between the two countries under consideration. To simplify the notation, however, the time variable and the country index are dropped from the following analysis.

Solow (1957) derived a measure for technological process, sometimes called Solow's residual. Applying the same assumptions and principles to the above production function, Solow's residual can be shown to be:

$$\frac{\dot{Q}}{Q} - \frac{\dot{K}}{K} - \tilde{b}_S\left(\frac{\dot{S}}{S} - \frac{\dot{K}}{K}\right) - \tilde{b}_L\left(\frac{\dot{L}}{L} - \frac{\dot{K}}{K}\right) = \frac{\dot{A}}{A}, \tag{A4.2}$$

where the dotted variables stand for derivatives with respect to time.
We denote the input shares simply as:

$$\tilde{b}_S = \frac{P_S S}{cQ} \quad \text{and} \quad \tilde{b}_L = \frac{P_L L}{cQ}, \tag{A4.3}$$

in which $\tilde{b}_S$ measures the share of R&D costs of the value of output, and $\tilde{b}_L$ stands for the share of the total labor wages of the value of output. The industry is assumed to be perfectly competitive and hence the output is valued at marginal cost *c*.

Under imperfect competition a firm's output is not valued at marginal cost, but the price exceeds marginal cost. Under imperfect competition, the shares of labor and R&D can be rewritten as:

$$\text{(A4.4)} \qquad \tilde{b}_S = \frac{p}{c}\frac{P_S S}{pQ} = \frac{p}{c} b_S \quad \text{and} \quad \tilde{b}_L = \frac{p}{c}\frac{P_L L}{pQ} = \frac{p}{c} b_L \ .$$

The terms b_S and b_L stand for the ratio of R&D expenditure to value added of production and the ratio of labor wages to value added of production, respectively. Substitution of the shares in equation 4 in Solow's residual in equation 2 provides:

$$\text{(A4.5)} \qquad \frac{\dot{Q}}{Q} - \frac{\dot{K}}{K} - \frac{p}{c} b_S \left(\frac{\dot{S}}{S} - \frac{\dot{K}}{K} \right) - \frac{p}{c} b_L \left(\frac{\dot{L}}{L} - \frac{\dot{K}}{K} \right) = \frac{\dot{A}}{A} \ .$$

We define the Lerner index for monopoly power as follows:

$$\text{(A4.6)} \qquad \lambda = \frac{p-c}{p} \text{ and } 1-\lambda = \frac{c}{p} \ .$$

Term λ stands for the Lerner index, that is the price-cost margin, and (1- λ) depicts the price-cost ratio. The generalized residual can be further rewritten as[1]

$$\text{(A4.7)} \qquad \frac{\dot{Q}}{Q} - \frac{\dot{K}}{K} - (1-\lambda)^{-1} b_S \left(\frac{\dot{S}}{S} - \frac{\dot{K}}{K} \right) - (1-\lambda)^{-1} b_L \left(\frac{\dot{L}}{L} - \frac{\dot{K}}{K} \right) = \frac{\dot{A}}{A}.$$

Multiplying both sides of equation A4.7 by (1- λ) and rearranging it, we get:

$$\text{(A4.8)} \qquad \left(\frac{\dot{Q}}{Q} - \frac{\dot{K}}{K} \right) - b_L \left(\frac{\dot{L}}{L} - \frac{\dot{K}}{K} \right) - b_S \left(\frac{\dot{S}}{S} - \frac{\dot{K}}{K} \right) = \frac{\dot{A}}{A}(1-\lambda) + \lambda \left(\frac{\dot{Q}}{Q} - \frac{\dot{K}}{K} \right).$$

If λ is zero, firms have no market power and Solow's residual (the left-hand side of equation A4.3) is technical change. If firms can price their products above marginal costs, Solow's residual depends on the changes in production and it fluctuates procyclically (the right-hand side of equation A4.8). This outcome forms a basis for the empirical setting provided by Chapter 4 above.

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[1] This also equals Hall's (1988) specification, which is the basis of his empirical estimation procedure.

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CHAPTER 5

RISK AND RETURN OF STRINGENTLY REGULATED DRUG DEVELOPMENT

Raine Hermans – Martti Kulvik

5.1 Introduction

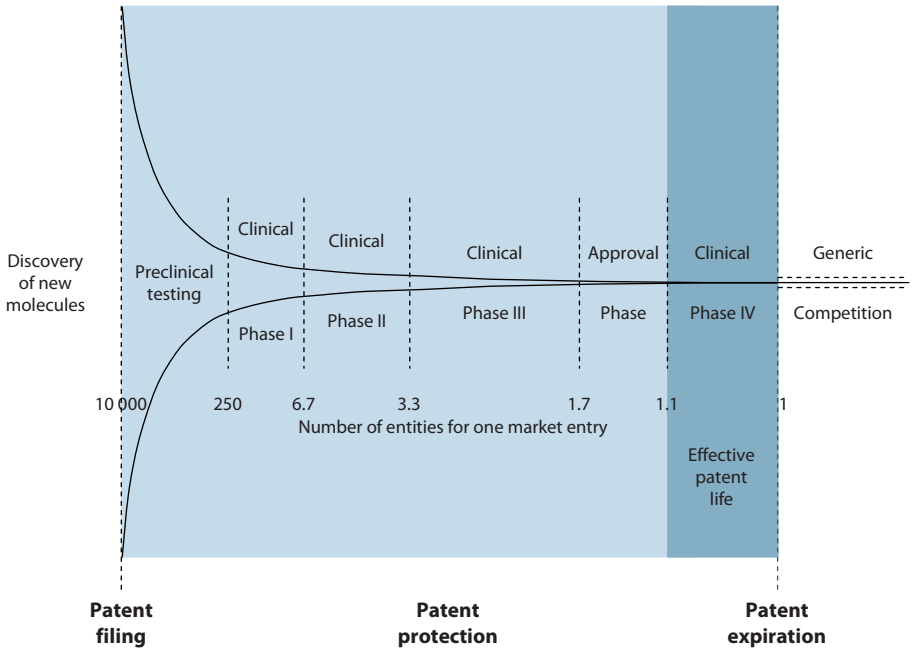
For any one new drug entering the market it is estimated that an average of 10,000 new entities have failed during any of the development phases. Moreover, drug development is strongly regulated to ensure maximal safety for patients. The requirements set forth by the regulation increases time needed for the development of the drug before it can be launched on the market. The value chain in drug development is challenging: the return sets on very late in the value chain, and the risks of failure at every step of the chain are significant (Figure 5.1). There is an imbalance between the R&D phase and the exploiting phase.

The previous chapters have dealt with the obvious trade-off between government support for the innovative healthcare industry and the expressed need for controlling healthcare costs, and drug costs in particular. In Chapters 5 and 6 a new perspective is added by drawing from the example of Finland's striving to establish a successful biotechnology-based drug industry.

This chapter takes a view into the future: the present value of the Finnish drug development activities is simulated. It is assumed that R&D expenditures are equal over countries on average (DiMasi et al., 2003) and the company's own anticipations were utilized as a proxy for the future sales.

Starting with a cross-sectional industry survey, this chapter uses a simulation that employs data from the portfolios of 46 separate development projects of 21 organizations covering approximately 80% of the Finnish bio-pharmaceutical small and middle-sized enterprises (SMEs) that aim to develop drug applications. Special

Figure 5.1 Number of projects in distinct drug development phases needed to generate a single application in the market



Source: US Congress, OTA, 1993; DiMasi, 2001a; DiMasi, 2001b; DiMasi et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006, and authors' calculations.

emphasis is placed on government and private venture financing requirements and their overall economic impacts. The results demonstrate that while focused project investments might make sense, because of the very small chance of success and the relatively large investment costs of the startup ventures, it is undesirable to create a vertically integrated bio-pharmaceutical value chain by using government subsidies as a main source of financing.

The early-stage drug development does not seem to be profitable due to the high risk of failure, which is, in turn, related to relatively high R&D costs. This implies a need for government intervention to activate early-stage R&D efforts to bring up seed technologies for later stage technology development and trials. Associating with pharmaceutical giants has proven to be one way of approaching a balance between risks and return on a more sustainable basis; likewise, the dedicated pharmaceutical companies have gone through a fierce vertical integration. The line between government and private financing requirements will be assessed more in-depth in the next chapter.

Three implications for innovation policies were identified: There is a need to develop tools for 1) steering the companies to utilize the special features and the exceptional resources of Finland and 2) controlling for the risks [of failure], and 3) emphasizing the solutions that also offer social benefits, as an argument for the public sector to bear the risks of development. These issues will be discussed later in this book.

5.2 Research setting

The drug development has been in a notable position in utilizing and funding biotechnology applications. There are many first-class research units and a unique patient database in Finland that create a strong base for domestic drug development. There have been considerable contributions to the drug development, even though the contributions have also been criticized by the public. The risk profile of the drug development is miscellaneous, and the development from a synthesized compound to a completed product has traditionally required considerable financial contributions over a long period of time. The drug development is in a state of change and the large international pharmaceutical industry is searching solutions for their problems from biotechnology. For example, the systematic synthesizing of compounds is being replaced with specialized synthesis based on target-specific modeling, and clinical research phases can be accelerated and partially replaced by information technology simulations.

In the drug development the large patient experiments of the clinical phase three typically rest on the shoulders of the large pharmaceutical companies, whereas the smaller companies act either in the earlier phases of the drug development or as a subcontractor for a larger company in the final stages of the development. The nature of the development essentially changes as the process of development advances. As the smaller drug developing companies are mainly concentrated on their own special substance, their value-creating strategies also vary considerably from one another.

5.2.1 Data and methods

This study simulates the growth potential of the Finnish bio-pharmaceutical industry, taking into consideration the different possibilities, with their risk levels, associated with the distinctive development phases at the micro-level. The companies in the simulation have identified themselves as biotechnology companies that

act in the pharmaceutical industry. The starting-point of the simulation was the strategies expressed by these companies themselves. The data are from these parts based on the biotechnology survey of ETLA, which has been described in detail in Hermans et al. (2006).

A simulation is a method which tries to imitate a real-world system that is mathematically too complex or too heavy to portray with other methods. One simulation method is the Monte Carlo simulation, which produces random values for uncertain variables and creates a forecast by using countless iterations (Drakos, 1995). The Monte Carlo simulation is applied in many fields, for example, in planning a nuclear reactor, in the radiation therapy of cancer, traffic flows, oil exploration, economic forecasts and contribution-yield models (Bullard and Sebald, 1988; Roland-Holst, 1989; Hermans and Kulvik, 2005). This study simulates the R&D expenses and profitability of the Finnish pharmaceutical industry, presuming that all the companies follow a uniform strategy in each scenario. Our basic scenario forms an exception, where each company is presumed to follow their own, self-expressed, unique strategy.

5.2.2 The Finnish pharmaceutical industry

ETLA, the Research Institute of the Finnish Economy, collected a unique database in 2002-2004 concerning biotechnology companies. Hermans and Luukkonen (2002) and Hermans et al. (2005) present a detailed description of the data. A forecast model built based on the database analyzes the economic and branch-specific growth-effects of the Finnish biotechnology industry (Hermans and Kulvik, 2005). The forecast model includes a risk profile of the biotechnology companies, which evaluates the bankruptcy risk and the probability of attaining the expected sales. The forecast model is argued at the economics level and gives a sufficient picture of the growth views of the industry in a small timeframe.

The small Finnish biotechnology companies have not yet been able to create significant sales. Based on the earlier ETLA projects it has nevertheless been possible to construct detailed risk profiles that take into consideration the composition of the product portfolios of the companies and the sales expectations relating to them; the reliable evaluation of the value creation potential of single companies, and the risks adherent to it, require knowledge of their value creation strategies.

The questionnaire from 2004 includes information about the product portfolios of 21 biotechnology companies whose product development is aimed at the pharmaceutical industry. These companies have 46 new chemical entities described in the database that are utilized in the drug development.

Table 5.1 Number of projects in different stages of drug development in 2005

Development phase	Number of projects
Discovery of new molecule	
Preclinical testing	33
Phase 1	3
Phase 2	7
Phase 3	3
Approval phase	0
Ongoing safety monitoring, Phase 4	0

Source: ETLA 2004 Survey (unpublished data).

Table 5.1 shows that the cross-section material used in the simulation clearly emphasizes the preclinical phase development projects. There are also 7 entities in the clinical test phase 2.

5.2.3 Building the simulation model: general presumptions

The starting point of a simulation, in addition to the drug development cost of each project, is the anticipated sales based on the sales anticipations expressed by each company. 30-50% of the income is supposed to be directed to the marketing of the drug (see Chapter 2), and the success of the marketing (real market potential + real penetration) has been estimated to vary between 50 and 100% of the companies' own estimates. The risk-adjusted net present value (rNPV; see Table 5.3) is used in the examination of the market values of the drug development projects.

The companies evaluated their new chemical entities' market potential and expressed their commercializing strategy for the innovations they possess. Their strategies and growth expectations have been proportioned to the figures from the pharmaceutical industry literature (US Congress, OTA, 1993; DiMasi et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006). The often referred to DiMasi et al. (2003) study, which examines 69 medicines from10 large pharmaceutical companies was used as a reference and starting point for the simulation.

The companies were each asked for the starting point of each project's patent coverage, which was used to calculate the duration of the coverage. For those companies that did not disclose when the patent application was filed, it was estimated to be on average two years from the start of the research project to grant the pat-

ent. The estimate is based on the research phases expressed by the companies: for example, the duration of research before entering the market must be closer to 8 than 15 years in phase 1. After the expiration of the project-specific patent coverage, the value of sales is anticipated to decrease to 20% of the sales during the last year of patent coverage (see *e.g.* Frank and Seiguer, 2003).

It is also possible to evaluate the average research expenditure for each phase of the project. In each phase the expenditure is iterated from uniform distribution as presented in Table 5.2 (US Congress, OTA, 1993; DiMasi et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006). The average time elapsed by each phase and the projects' average probability of success is also derived from the literature (US Congress, OTA, 1993; DiMasi, 2001a; DiMasi, 2001b; DiMasi et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006); this information is added to Table 5.2. The probability of success can also be illustrated as follows: for one successful chemical entity, an average of 10,000 chemical compounds need to be sifted, 250 of which go through the animal tests of the preclinical phase and to more accurate chemical analyses. Five of these proceed to clinical patient research phases, and in the end one medicine is approved for sale on the market.

The phase 3 research expenditure of approved drugs estimated by DiMasi et al. (2003) is USD 115 million and for all the frames the cost is USD 86 million. The Pharmaceutical Research and Manufacturers of America (2006) add a distinctive

Table 5.2 The development time required by each project, the probability of success, and the average cost of development by phase (Eur, year 2000 prices)

Development phase	Years taken by a phase	Probability of success	Average expenditure of a phase	Median expenditure of a phase
Discovery of new molecule	5	0.01 %	6,050	4,000
Preclinical testing	3	0.40 %	242,000	195,000
Phase 1	2	15.00 %	15,200,000	11,700,000
Phase 2	2	30.00 %	41,700,000	31,500,000
Phase 3	3	60.00 %	86,300,000	62,000,000
Approval phase	2	90.00 %	29,000,000	17,000,000
Ongoing safety monitoring, Phase 4	8	99.00 %	140,000,000 (during 8 years)	90,000,000 (during 8 years)

Source: US Congress, OTA, 1993; DiMasi, 2001a; DiMasi, 2001b; DiMasi et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006, and authors' calculations.

regulatory approval phase and expenditure to the phases. The regulatory approval is taken into consideration in the simulation so that the projects that have passed phase 3 still go through the authority approval, but the total cost of the phase 3 of the simulation and the authority approval equal the DiMasi et al. (2003) phase 3 costs.

The uncertainty of the expenditures is estimated in the simulation by using triangle probability distributions that match the DiMasi et al. (2003) estimates for means and medians. Then the minimum and maximum within the distribution include 95% probability mass of the distribution; the figures less than the mean value are the most probable. This way the basis of the simulation is a range of variations as close to the real drug development costs as possible, and thus the variation of the expenditures in Table 5.2 portrays the most probable cost structure in different phases.

After entering the market there is still the risk that in wider use some non-desired features are revealed in the medicine; these may lead either to a restriction of the use-indications or even to a total removal from the markets. The business activity risk related to the continuous safety surveillance was taken into consideration with a careful 1% failure probability after entering the market; for example, Brännback et al. have presented an approximately 2.5% risk for the same phenomenon (Brännback et al., 2005). To take into account the time-value of money, the calculations also include a 2% annual inflation rate in accordance with the monetary policy target of the European Central Bank. All results have been converted into 2000 prices.

It can be seen from the results that the expenditures rise rapidly in the last phases of the approval process of a medicine. The preclinical research can be financed with a quite modest contribution (less than 1 million euro per project), whereas third phase clinical research, authority approval, and continuous safety surveillance cost 205-371 million euro per company. The figures used in this simulation are in line with the out-of-pocket expenditures analyzed by DiMasi et al. (2003), which are lower than the total expenditures.

15% has been taken as the risk-free discount rate, which is slightly lower than the rate used in the USA for the industry. Bank loan based financing is practically out of the question for small biotechnology companies, and the most probable financers are venture capital investors and large pharmaceutical companies; the IRR for them has typically been 20% when the WACC is 9% (Moscho et al., 2000; Stewart et al., 2001; Hermans et al., 2007). The discount rate of 15% chosen best illustrates the Finnish public sector emphasized investors' relatively more modest profit expectations.

By combining the discount rate with the projects' probability of success, the risk-adjusted discount rate of the potential financers can be derived (Table 5.3).

Table 5.3 Risk-adjusted discount rate by phases

	Preclinical testing	Phase 1	Phase 2	Phase 3	Approval phase	Ongoing safety monitoring, phase 4	Marketing
Risk-adjusted discount rate, %	99	44	41	36	28	15	15
Probability of success, %	0.4	15.0	30.0	60.0	90.0	99.0	100.0

Source: Moscho et al., 2000; Stewart et al., 2001; Hermans et al., 2007, and authors' calculations.

The risk-adjusted discount rate is almost 100% in the early stages of the research but it drops quickly as the project moves on to the next phases. Finally, the risk-adjusted discount rate of an ordinary pharmaceutical company that does the final research and marketing is on average 20% (Moscho et al., 2000).

5.2.4 Simulation of the economic effects of distinctive strategies

The figures presented above and the probability distributions of the model were used in a Monte Carlo simulation which iterated the model 10,000 times and as a result produced the probability distributions for the second phase. The model covers the whole drug development cycle of the companies, including the phase-specific probabilities of success.

The simulation takes into consideration the alternative development paths with which the growth effects of different business models have been evaluated. Five different business models have been examined in the simulations and their conclusions.

I A Finnish biotechnology company continues commercialization according to the strategy it expressed in the survey.
II A Finnish pharmaceutical company buys or licenses the research projects of the biotechnology companies and the research is completed in Finland.
III The intellectual property rights are licensed abroad before the most expensive development and marketing phases.

The stocks are sold abroad and

IV The research continues partially in Finland.

V The research is transferred abroad.

In sections 2-5 the forecast produced by the first model is compared to the economic impacts of different commercializing strategies. The models offer an opportunity for the quantification of the impacts of the different strategy options based on the micro-level company data. The micro-level data are the essential prerequisite for the branch-specific modeling and constructing alternative scenarios.

The distributions produced by the simulations can be interpreted as examples, a means of illustrating the possible economic impacts of different strategy options from different perspectives. Numeric figures should not be interpreted as real or euro-amount forecasts because the simulation presumes, with the exception of the first scenario, that in each review all the projects have identical strategies. Regardless of these reservations, considering technology policy evaluation and planning, the project gives the best estimate in hand of the Finnish bio-pharmaceutical SMEs' drug applications' current net values taking into consideration the scenarios of different development phases.

5.3 Results

The results of the simulation are presented by each strategy option. In addition, each strategy group has been divided to two periods: from 2005-2009, and 2005-2015.The sales predictions disclosed by the pharmaceutical companies themselves extend to 2008, after which the sales are presumed to remain at the same level. In scenarios III-V, all the anticipated sales to the end of 2025 have been derived from the estimated royalty incomes of the companies.

5.3.1 Scenario I: a Finnish biotechnology company continues the commercialization according to the strategy it expressed

Period 2005-2009

Presumptions

- ETLA's survey data of the anticipated sales of the companies following their own strategies

- probabilities of success (DiMasi, 2001b; DiMasi et al., 2003)
- R&D expenditure (out-of-pocket type, US Congress, OTA, 1993; DiMasi et al., 2003, Pharmaceutical Research and Manufacturers of America, 2006; table 5.2)

All of the companies disclose receiving sales revenues from their projects before entering the market. On this basis it can be presumed that all projects will be licensed at some point in their development, probably to cover the development and marketing costs and thus control the risks. Because the relative development costs essentially increase when the projects proceeds to the next phase, presumably most of the development costs are redirected outside the company and the domestic pharmaceutical sector. The model takes into consideration that when the project fails the expenditures also cease. It is presumed that the share of the Finnish pharmaceutical sector will be at 20% of the total costs.

As a result of the simulation, the R&D expenditures for 2005-2009 almost follow a normal distribution (Figure 5.2). From the result it can be seen that the distribution of the R&D expenditures of the companies is quite dense, and the R&D expenditures vary between 210 million and 415 million euro during the simulated five-year period.

Figure 5.2 R&D expenditures (2000 prices) for the period 2005-2009

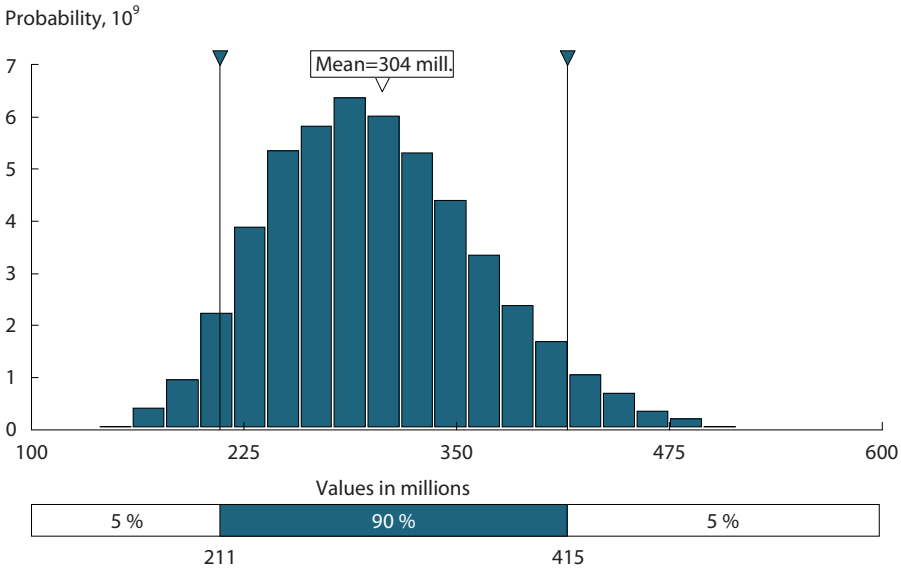
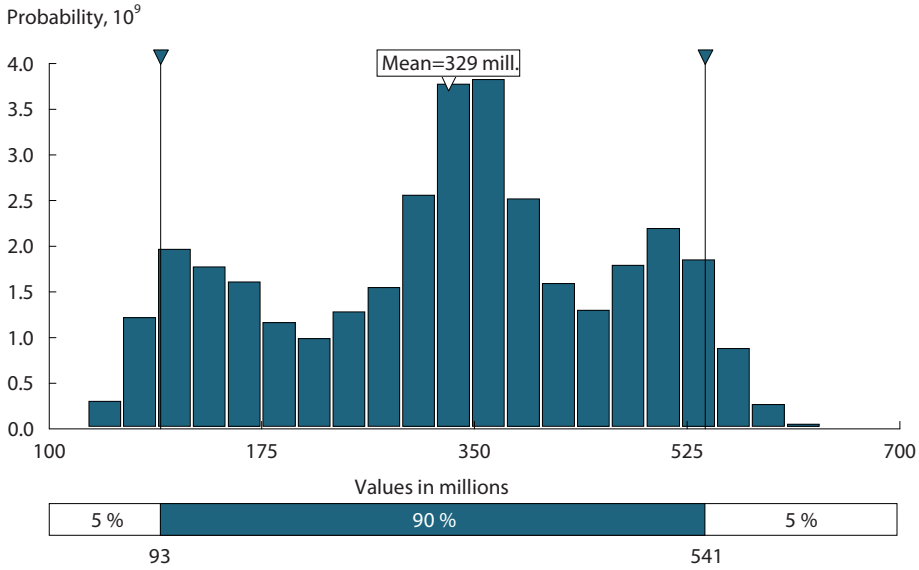


Figure 5.3 Value of sales (2000 prices) for 2005-2009



Instead of the above finding, the anticipated income from the projects is dissolved very widely into three parts (Figure 5.3), reflecting the uncertainty of the success of the sales. The scenario extends the early-stage either-or–situation to the whole industry: in addition to the potentially successful future, alternative scenarios, which express the realization of the inevitable risks of the industry, can be found in the Figure.

Subtracting R&D expenses from the sales (royalty incomes) yields the net sales for 2005-2009 (Figure 5.4). The R&D expenses are presumed to remain at 0-20% of the total expenses after the licensing or the collaboration agreement. Marketing expenses were not subtracted from the sales because all the strategies include the licensing outside the company so the incomes are straight royalty-incomes. The probability of the net sales of the companies in the data being positive in the calculations extending to the end of the decade is holding below 5%.

Period 2005-2015

In the scenario extending to 2015 the R&D expenses do not change decisively compared to the shorter period (Figure 5.5) because a substantial part of the R&D activities is transferred to foreign operators by the end of the decade.

Figure 5.4 Net sales (2000 prices) for 2005-2009

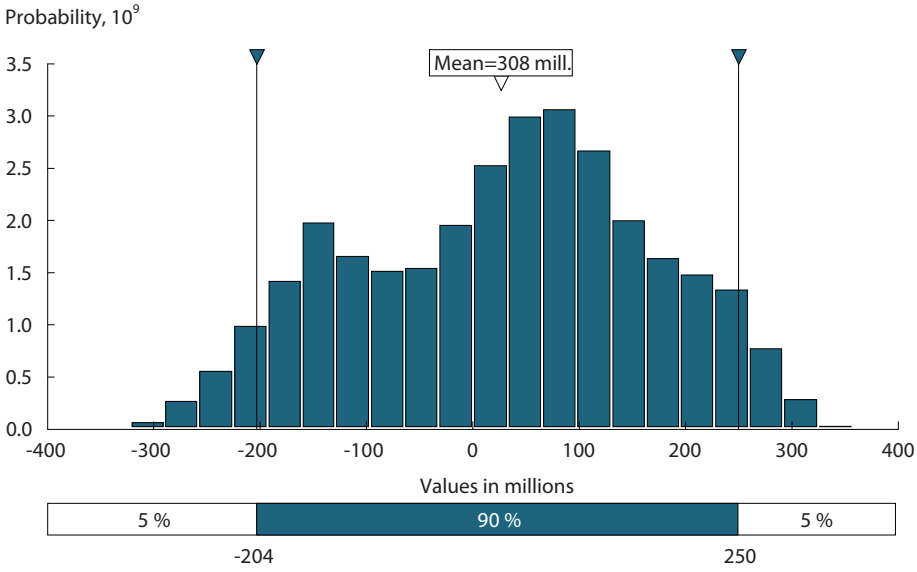


Figure 5.5 R&D expenditure (2000 prices) for 2005-2015

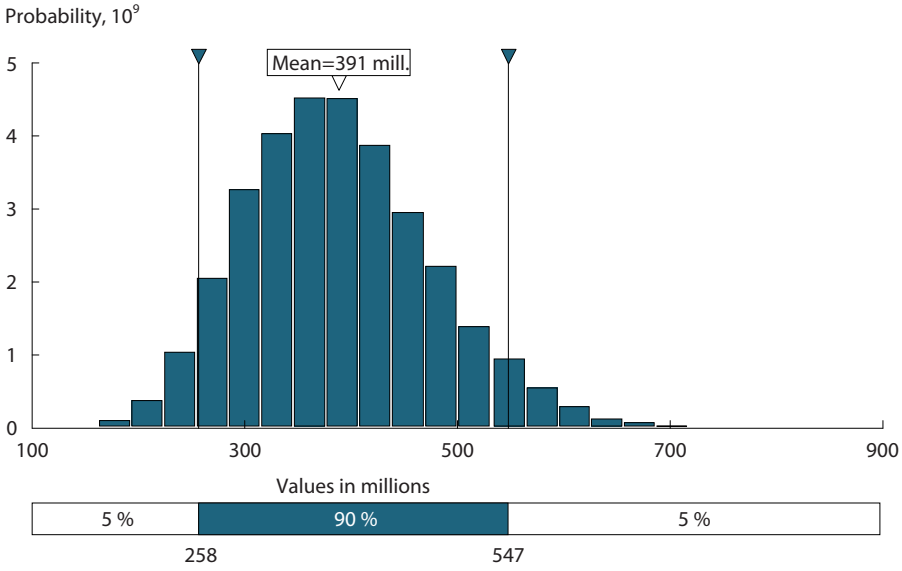
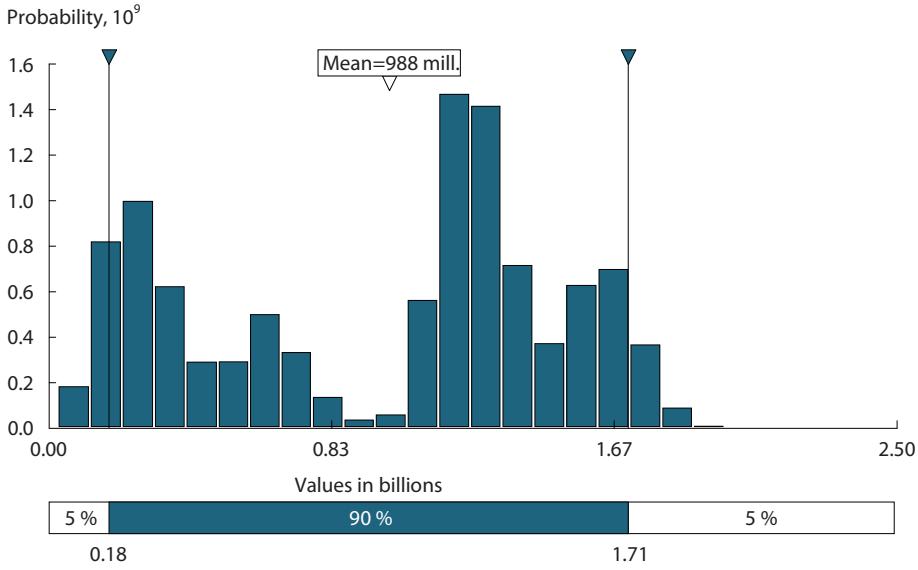


Figure 5.6 Value of sales (2000 prices) for 2005-2015



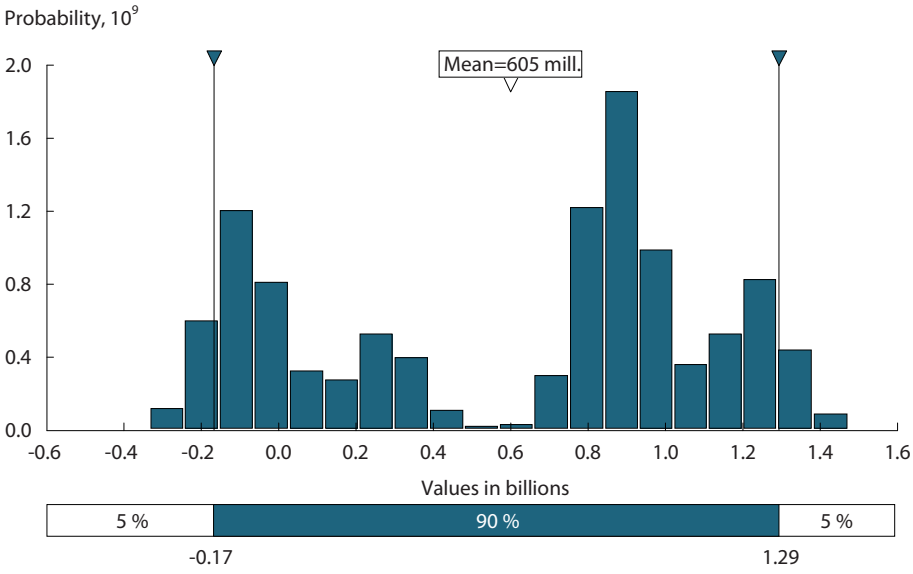
The anticipated sales shown in Figure 5.6 have more strongly divided dichotomically than in the simulation of the shorter period above. The anticipated total sales have accumulated more and thus the mean of the sales is approximately triple that of the above.

The scattered probability mass can also be seen in the net sales, which emphasizes the different expectations of single project groups (Figure 5.7). The dichotomy of the distribution also is emphasized by the decreased number of projects at the end of the period under examination.

The expenses take place, relatively certainly, in the early stages of the period, whereas the more uncertain sales will not take place until the final stages. This equals an increase in the risk of delays of net sales. Thus the success of a few products causes a significant growth in net sales, but the failure or complete transfer abroad of a few single projects may make the total net sales of the Finnish industry negative.

In the next chapter the scenario in which the domestic pharmaceutical industry aims at developing the drugs all the way to the end is studied. In the same context the structure of risks is also examined in detail and the risk-adjusted NPV brought to the simulation as a new element to valuate the effect of single successes or failures to the net sales and evolution of the simulated current value of the industry over time.

Figure 5.7 Net sales (2005) for 2005-2015



5.3.2 Scenario II: the Finnish Pharmaceutical company

In the models simulating the scenario presented in this section, a single Finnish pharmaceutical company purchases or licenses every R&D project of other biotechnology companies and thus the projects are finished in Finland. This strategic option could be described as Finnish Pharmaceuticals Plc. The basis of the strategy could be the intent to maximize the domestic share of the potential increase in value of the drug development projects. The significant increase in value of the project in the end of each successful phase makes such a strategy attractive. The downside of the strategy is the rise of the contributions required and thus the risks in the beginning of the phases. In economic literature this setting can be illustrated as betting with rising stakes (see e.g. Stewart et al., 2001 which studies the biotechnological drug development projects' valuation for the investor). In the next theoretical setting the financial contributions required by both periods are first studied and then the corresponding NPVs.

Estimated expenses for 2005-2009

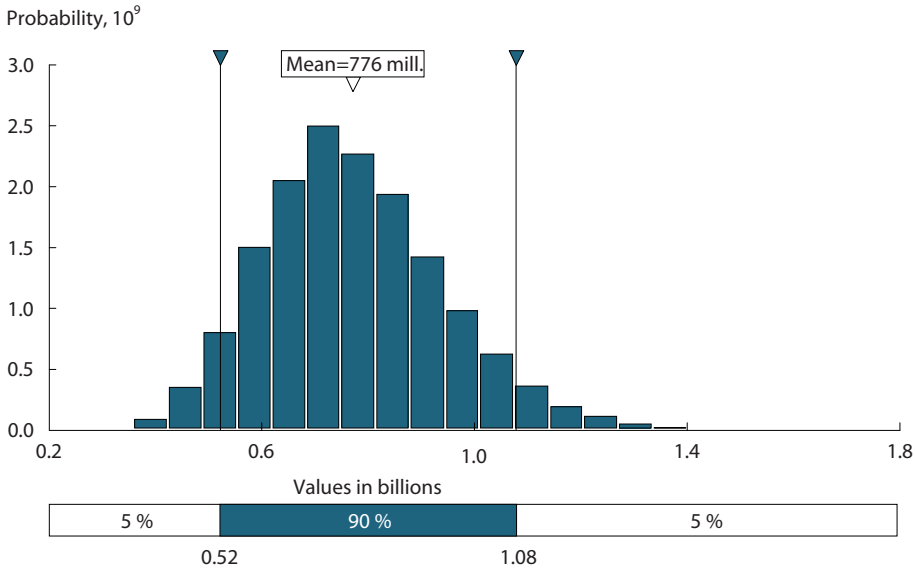
If all 46 drug development projects in this study were finished in Finland, approximately 760 million euro (2000 prices) would be needed in development contributions for 2005-2009 according to this simulation. The R&D contributions of the drug development would be between 520 and 1,070 million euro with the probability of success at 90% (Figure 5.8). The triangle probability distribution is similar in shape to a normal distribution as in Figure 5.1, but the necessary contributions are approximately triple compared to that. The similarity to the normal distribution of the R&D expenses illustrates the "certainty" of the expenses.

Estimated expenses for 2005-2015

In a longer period, the expenses still rise, varying between 750 million and 1.8 billion euro at the 90% significance level (Figure 5.9).

Thus completion of every project would require a contribution of at least 750 million euro and at most 1.8 billion euro during the next eleven years; this would

Figure 5.8 R&D expenses (2000 prices) for 2005-2009



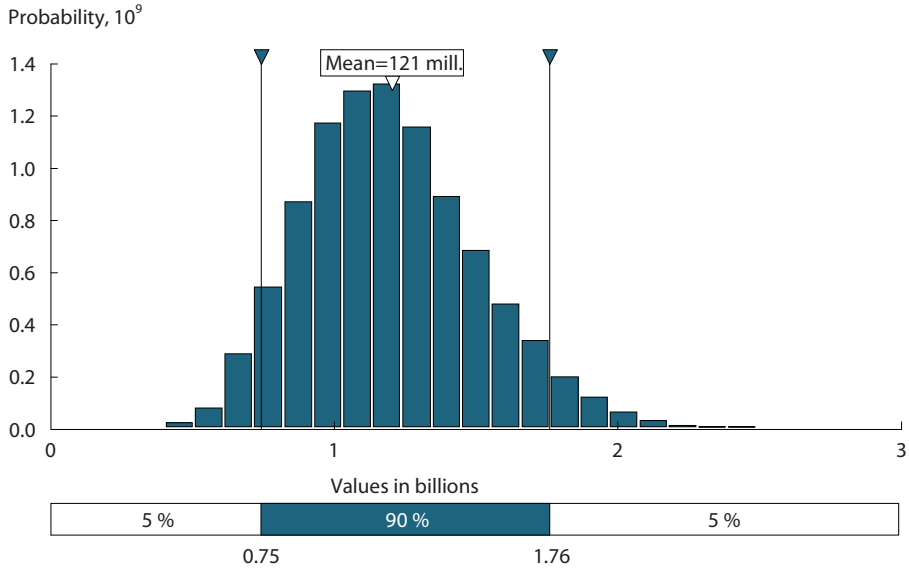
require on average 75 to 180 million euro in annual contributions over the next ten years (in 2000 prices).

These estimates include only approximately 80% of the Finnish pharmaceutical companies; inclusion of the whole project portfolio would slightly increase the necessary contributions.

Risk-adjusted net present values

The risk adjusted net present value (rNPV) evaluates the anticipated sales potential and the R&D expenses of a drug development project as a whole. The results can be interpreted as a forecast produced by the simulation portraying the simulated value of the Finnish drug development projects of the entire industry. If all the projects were sold to one operator or the R&D were performed, for example, by one publicly listed company, the rNPV would portray the simulation-produced market capitalization of the company. The levels of market capitalizations are comparable because they have been systematically reported in year 2000 prices. The simulation takes into consideration the expiration of patent coverage and the decrease of sales to 20% from the level it was during the coverage (Frank and Seiguer, 2003).

Figure 5.9 R&D expenditures (2000 prices) for 2005-2015

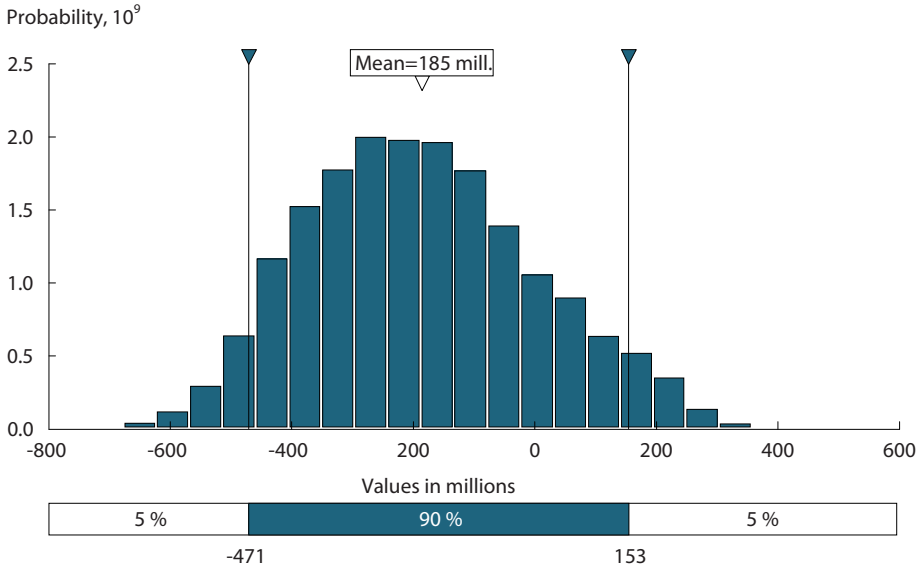


The Finnish biotechnology industry is relatively young; the pharmaceutical companies of the 2003 survey had no medical compounds of their own in the pharmaceutical markets. The early stage of the research projects can be seen in the 2005 risk-adjusted NPV-simulation as an inclined distribution, which is, in addition, clearly emphasized on the negative side (Figure 5.10). A young industry branch also includes many risks from the investor's point of view, which is reflected in the high discount rate (Table 5.3).

The negative NPVs in the simulations can mostly be explained by the fact that over two thirds of the projects under examination were in the preclinical phase in 2005. The risk-adjusted discount rate used for the preclinical phase projects dilutes the NPVs of the uncertain earnings in the distant future in the simulation. The further in the future and the more uncertain the earnings, the less the investors value them in the early stages of the R&D.

According to the simulation the market capitalization of the whole bio-pharmaceutical SME sector would be negative in 2005. If the investors use discount factors similar to those used in the simulation in their valuation schemes and if they expect quick returns over 3-5 years, it would be very difficult, if not impossible, to see any private investment injections that would support the whole industry.

Figure 5.10 Risk-adjusted NPVs (2000 prices) in 2005



The investor would be very careful in picking up a single project – most probably expecting years to come and later phases of the project.

In the end of the decade the distribution is even more inclined, but at the same time it has become positive as a whole (Figure 5.11). The simulation foreshadows that the interest of the investors and the stock markets towards the drug development projects that continue their work would be relatively large in the end of the decade. The considerable wideness of the rNPV distribution portrays the risks related to the development of market capitalization of the entire industry.

In 2015 the market value anticipations are fairly similar to those five years earlier. The positive tail has slightly lowered as the end of the anticipated lifetime of the projects draws near (Figure 5.12). The maximum limit of the market value still remained quite high because the survived projects function as "milk cows": a few years of anticipated sales remain when the R&D expenses are already over.

When interpreting the results of the rNPV simulation it is important to notice that the results presented do not portray the profitability of any single project, the industry is studied as a whole. The failure of many projects would cause a considerable inclination towards the losses: the R&D expenses are realized early and if the project fails, the anticipated sales will not happen. If there are many of these early stage projects, the NPV remains negative as a whole.

Figure 5.11 Risk-adjusted NPVs in 2010

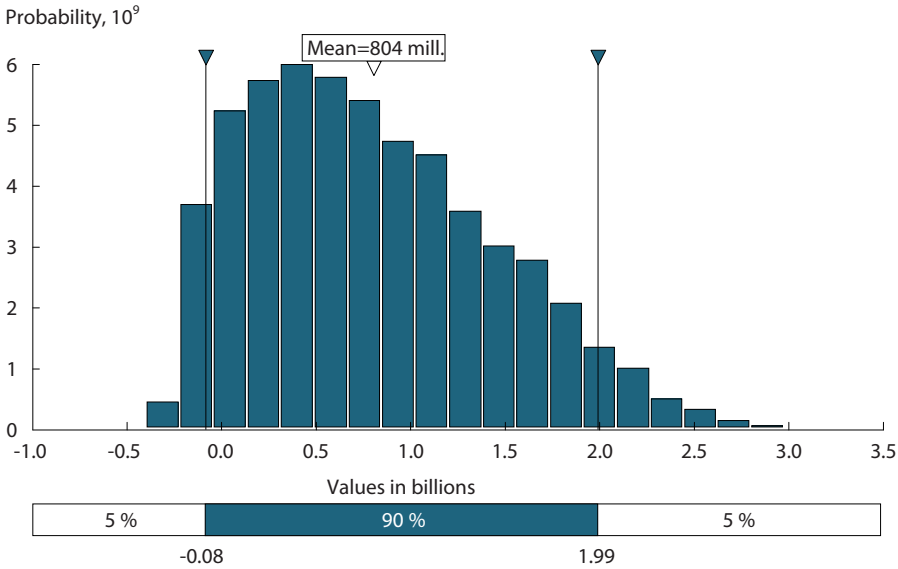
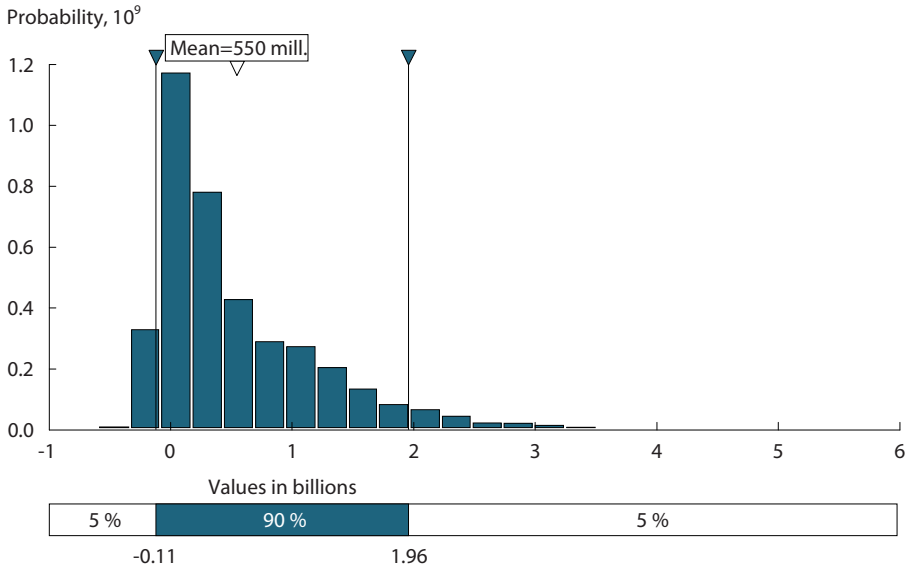


Figure 5.12 Risk-adjusted NPVs in 2015

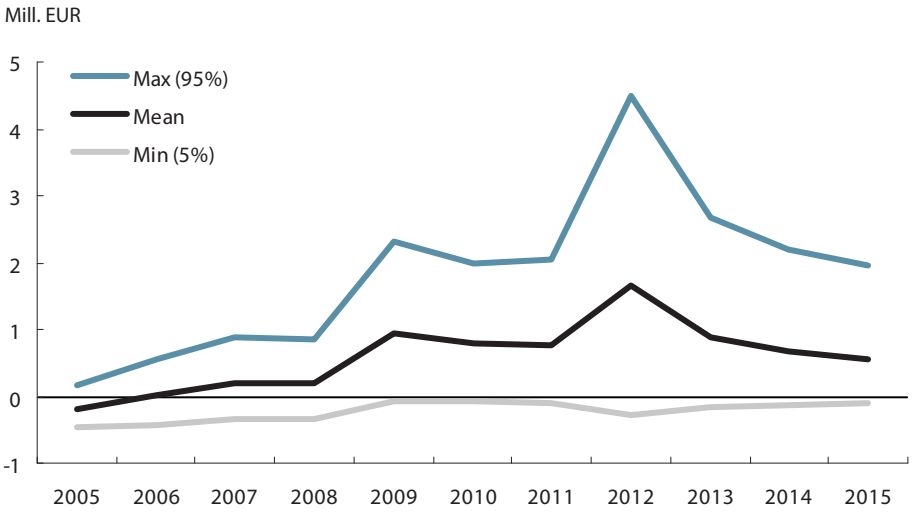


The development of the simulated market value of the entire industry (or Finnish Pharmaceuticals Plc) is presented in Figure 5.13 for 2005-2015. The market capitalization is negative at the start, but begins a steady climb as the projects progress in the drug approval process and some end. According to the simulation, the investors would evaluate the highest market capitalization of the current projects to be in 2012-2013. Then two or three projects that were in the early stages in 2005 get the regulatory approval and enter the markets. Then the market capitalization begins to fall as the expiration of the patent coverage for the products draws relatively near.

The simulation portrays the considerable discount rates and risks of the industry going side by side. As the simulation generates a 5% probability for the projects under examination to have a market capitalization of several billion euro in 2012 (the upper limit in Figure 5.13), it also produces a 5% probability for the Finnish drug development industry not to reach positive market capitalizations even in 2015 (the lower limit in Figure 5.13).

Considering the strategy, the simulated development of the market capitalization of Finnish Pharmaceuticals Plc means that new projects should be continuously under development if a certain level of market value is to be maintained. If, in part,

Figure 5.13 The rNPV of Finnish drug development projects in simulations in different years



only the current projects are taken care of, the volatility of the market capitalization can be expected to be relatively large. Thus, developing new projects decreases volatility and increases the absolute monetary values of contributions and possible incomes in each scenario, but does not affect the probability of success of single projects or shorten the development time.

Assuming that the average structure of the projects does not alter, the situation can be related to raising the stakes when the number of operators decreases. If, however, learning occurs or in some other way the previous development can be utilized in a way that crucially improves the risk management of the development work, the outcome of the development can be positively affected.

It should be mentioned that the argumentation above, considering the number of projects, can also be generalized to other scenarios.

5.3.3 Scenario III: the intellectual property rights are licensed abroad before the most expensive development and marketing phases

Our project-specific data revealed that the companies mainly use such a strategy (compare to Scenario I: A Finnish biotechnology company continues commercialization according to the strategy it expressed). Thus the simulation of this basic choice is already done above.

5.3.4 Scenario IV: the stocks are sold abroad and the research is not continued in Finland

In practice, the companies or their technologies would be sold abroad one by one and at different times. In this context the bio-pharmaceutical SME sector must be studied as a whole, *en bloc*, so that a picture of the value development of the industry as a sector might be formed. According to this the rNPV calculations in Figure 5.13 portray the calculated market value of the projects under examination at different times. The rNPV calculations can be interpreted as imaginative investors' estimates of the market capitalization of the whole sector at respective times. Thus the simulation studies the development of the value of the industry as a whole, on the principle that someone would buy the entire remaining portfolio.

According to the results of the simulation, the selling price of the projects remains relatively low in the beginning. The total market capitalization of the projects reaches the one-billion-level by the end of the decade, but there is also a 5% probability that it is clearly negative. If the negative rNPV is real, it can be interpreted that the investors would not be interested in the projects under examination, at least in their entirety.

The investor might want to time the investment for when a considerable amount of the R&D expenses have already been paid. The bid price is relatively low in 2007-2008 but the projects still require considerable investment. The simulation portrays the value increase to be greatest in the upcoming years and at the end of the decade, and a significant decrease in the number of projects is also to be expected in the near future. This leads to the decrease of risks directed at choosing the projects. In other words, the significance of information asymmetry between the entrepreneur and investor decreases.

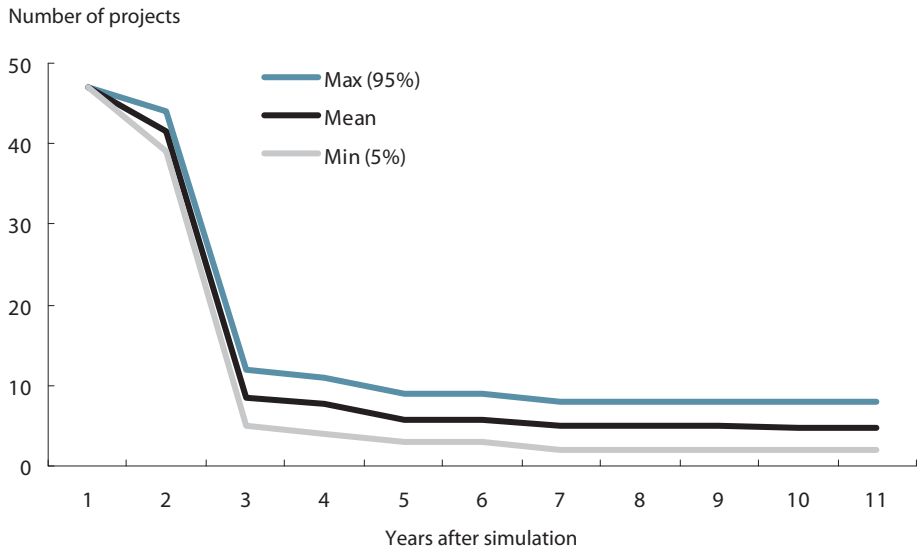
2012-2013 is the most positive scenario of the simulation, at the threshold of the greatest value increase. A significant part of the R&D expenses have also already been realized and thus the total risk level can be more clearly controlled. The whole

pharmaceutical industry under examination has contributed from one half to one billion euro to R&D in the simulation (Figure 5.8). The market value of the sector in the simulation is on average slightly below 1.5 billion euro. However, according to the sale scenarios above, the probability of success of the sector is very bipartite. In the most positive scenario the R&D contributions can be covered, while in the negative scenario the rNPV is negative, lowering the willingness to invest.

The number of current and forthcoming projects at the time of the survey (2004) will decrease fast over time (Figure 5.14). In the end of the decade, according to the simulation, fewer than 10 projects are still functional. This illustrates how the success of the industry is reduced to the success of single projects and to the strategies the entrepreneurs choose for them.

On average only five of the chemical compounds entering the preclinical phase proceed to clinical research and one gets to markets (DiMasi, 2001b; Pharmaceutical Research and Manufacturers of America, 2006). As the pharmaceuticals in Figure 5.14 are at the end of their development, the model is considerably insensible for the number of projects in the early phases: 250 new compounds in the preclinical phase increases the number of projects in the end by one. Thus the central issue is the skilled risk management discussed earlier and especially the ability to recognize the compounds that are less likely to succeed as early as possible.

Figure 5.14 Number of projects over time



From the investor's as well as the public sector's perspective the timing is associated with the risk management. When the companies or their technologies are sold, in the early phases the probability of getting significant capital gains or tax revenues is lost. But if the NPV of the industry is negative (lower limit of Figure 5.13), the (international) investors are unwilling to make investments. Then the public sector must decide, if it wants to take some of the risk of the sector.

In weighing the risks and the anticipated earnings , the public sector may also consciously choose a course different from a private investor, which is discussed further in Conclusions below.

5.3.5 Scenario V: the stocks are sold abroad and the research is partly continued in Finland

This scenario is built by combining the NPV-calculation portrayed above (Scenario IV; Figure 5.13) and the simulations from the first scenario following the companies' own strategies. In strategy option 1 the companies were presumed to continue their research in Finland, but most of the R&D in the later phases was transferred to [foreign] collaborators. In this case the [foreign] owner transfers money to the R&D in Finland through transfer pricing. This can be presumed to be equal to scenario 1 regarding expenses.

The problem of the sector in the whole scenario is still the attractiveness of the industry in the NPV sense. If the rNPV is positive, and if the projects are sold relatively early, most of the risk is transferred to the foreign investor. On the other hand, the anticipations also related to the value increase of the portfolio are realized abroad.

5.4 Conclusions

This study simulated the development of the bio-pharmaceutical SMEs in Finland, assuming that the entire sector utilizes similar financial models and business strategies. In reality, however, the assumption of all companies adopting similar business strategies is unlikely. Hence, the results of the simulation should not be interpreted as exact forecasts of the development of the industry, but rather as a tool for comparison and assessment of the finance and business activity risks.

It should also be emphasized that this simulation concerns medical applications of bio-technological companies only. The results can and should not as such

be generalized to other bio-technological applications and companies since their value creation logic often follows quite a different path.

The value of the results of the simulation relates to the basic assumption of the simulation: are the implemented pharmaceutical development and marketing expenses adequate for this setup? If, for example, the pharmaceutical expenses in Finland were substantially different from those of the rest of the world, the estimates of DiMasi et al. (2003) should not be used.

On the one hand, DiMas out-of-pocket expenses was used, which for the clinical research phase constitute only about half of the actual capitalized expenses and hence even underestimate, not overestimate the expenses. On the other, there are also examples suggesting that the Finnish pharmaceutical development has been able to carry out clinical experiments in foreign countries with lower costs than average, and there are estimations suggesting similar results for domestic trials (Kurkela, 2006; Brännback et al., 2005).

It becomes evident that at the corporate level a skilful assessment and selective exclusion of R&D-projects is crucial. A few original medical compounds have been successfully developed for international markets in Finland, with significantly lower development costs.

A further issue is whether the technical risks are better controlled in Finland than in foreign countries; are low-profit projects identified and terminated at a very early stage? The pharmaceutical development projects in this material do not seem to verify such an assumption, because the projects in different phases seemed to be relatively old. On the other hand, a clear majority of the development projects were in the preclinical phase, which in itself may indicate an active termination of projects at later stages. The material is a cross-section, and therefore the ability of companies to control for technical risks cannot be directly assessed based on this data alone. [Dynamic examination could be reached by executing a final-stage survey, in which one charts how the announced projects actually succeeded, and comparing this information to the already collected data of companies' evaluations in 2002 of their selling in 2006.]

Marketing and distribution add significantly to the total costs of drug development. The small size of Finland could be compensated for if Finland had a global scale industry that supported and was interested in drug development and marketing; however, Finland has no BioNokia. The lack of a domestic pharmaceutical industry leads to a shortage of international managerial experience, aggravated by the lack of pre-existing distribution channels to the global markets. This might lead to a deleterious combination where the Finnish companies might overestimate their true market penetration capability and underestimate the international rivals' ability to utilize the market potential.

There are only a few active knowledgeable biotechnology financiers on the Finnish markets. The lack of a large supporting pharmaceutical industry may also reduce other financiers' interest in the Finnish biotechnology sector. Consequently, for Finland's relatively small bio-industry knowing financing markets may form a risk of even good projects being terminated due to an absolute shortage of available funding.

The lack of a supporting industry may lead to the bio-industry financiers being left economically inexperienced, with a risk of picking out technologically interesting and scientifically convincing, but economically and strategically weak objects. Moreover, the relative inexperience of both companies and financiers may stimulate the companies to continue expensive clinical testing despite doubtful results: if the clinical results are interpreted unrealistically, the companies become unable to cease funding at an early enough stage.

In this study the companies' simulated market capitalization is at its peak when the early stage projects enter the pharmaceutical markets in 2012-2013. If the drug development projects were completed in Finland and each project sold abroad only after completion of clinical trials, the state would gain several hundred million euro in tax income. Before this, however, several hundred million would have to be invested in a larger number of projects, thus equalling expenditure and yield.

For an accurate interpretation of the distribution in the simulation, it is essential to notice that the risks are also significant. The mean values cannot be used in themselves, because the probability for success is very dichotomously distributed. The lower boundary of the market value (5%) will not reach a positive value until 2015, while the higher boundary is several billion euro positive. It can be concluded indirectly that the anticipated growth of the 2012 market value also predicts a downward curve of the lower boundary: great profit expectations come with great risks.

If the lack of supporting industries hampers completion of pharmaceutical development in Finland with the research and marketing consequently being completed abroad, the market value forms an essential indicator for the benefits gained from the projects, both from the entrepreneur and the public sector's perspective . Instead of active entrepreneurship and new jobs, the simulated drug development projects will generate capital tax incomes compensating for earlier investments made by the public sector, equal to the scenario above.

For Finland the most tempting situation within a balance between part of the research staying in Finland, but risks transferred to large-scale companies in foreign countries by selling either fragments of projects and companies or whole entities abroad. The research and development in Finland generates benefits in both employment and domestic know-how, and part of the investments and taxes remain

in Finland. After successful projects the Finnish companies will also gain funds to cover the development expenses of new projects. Indeed, the partial continuation of research and development in Finland seems to have been the main strategy of Finnish drug development companies. Consequently. the main question becomes: how can Finland attract R&D to stay in Finland, even partially?

There turned out to be only a few projects left at the later stage of the simulation. Consequently, the development of the market capitalization is dependent on which single projects will ultimately be carried forward. Moreover, the probability distributions within each year are very lopsided, with the biggest probability mass being situated near zero but including a long tail with high market values.

The simulation indicates that drug development is associated with great profit expectations, but the chances of failure in business and technological development are significant even evaluated at the entire industry level. The crucial challenge for the Finnish drug development companies is how to proficiently control for the risks.

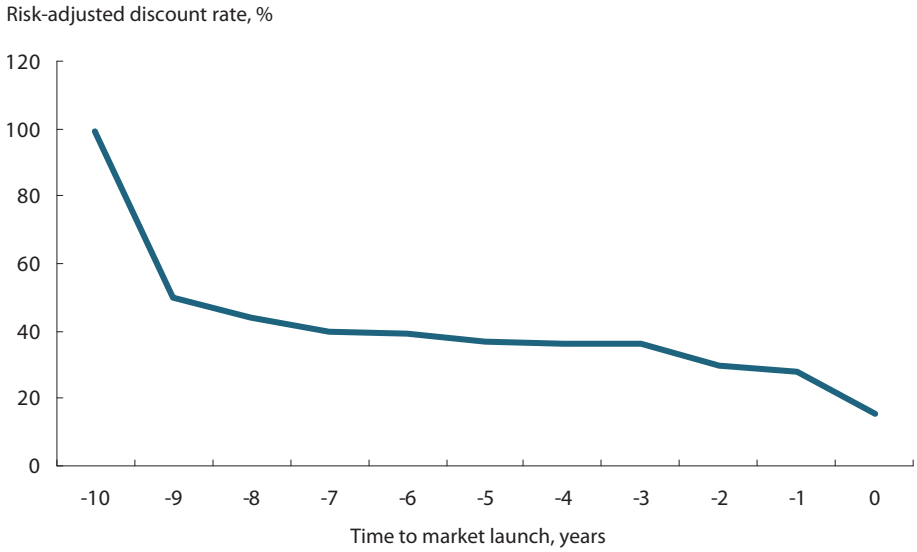
A further interpretation from the results of the simulation is that the government of a small open economy should not necessarily only mimick their larger counterparts, but instead focus on acitivities that are based on a sound reasoning within the global value chain. This approach has been the basis for a domestic biotechnology strategy prepared with the participation of the Finnish industry and commerce, the public sector, and the scientific community (Hermans and Kulvik, 2006a, 2006b) Chapter 9 in this book presents a further development of this strategy.

Appendix 5

The role of the public sector in drug development: a case study drawn from the simulation

Investment activities taking high risks calls for high profits; the risk-adjusted discounted interest at the preclinical stage of drug development is nearly 100%, and in the new entity discovery phase up to a decade higher (Tables 5.2 and 5.3). Such high discounted interest reduces the net value of pharmaceutical development projects in the preclinical stage to a level where development costs are no longer rational to cover with private funding; the required investment at the early preclinical phase is higher than the risk-adjusted value. However, when the project approaches clinical trials, the discount interest's (and risk's) significant decline makes private funding also reasonable. Figure A5.1 presents how the risk adjusted discount interest evolves over time in such an average pharmaceutical development project where additional funding is infused during each phase, and where net value is equal to the capitalized total cost at year 11.

Figure A5.1 Risk-adjusted discount rate of average drug development project over time. Time 0 depicts the market launch of the drug.



A complementary approach is shown in Figure A5.2, where the investment's risk-adjusted present value and respective holdings are presented phase by phase, with an endpoint of the medicine being established on the market, and assuming that the development costs can be covered. Each project entering the market has been preceded by approximately 10,000 new chemical entities, out of which 250 have proceeded to the preclinical stage (chemical and animal toxicity experiments), and 5 to the clinical stage.

It is assumed that a virtual company takes over the drug development as soon as the molecule has been identified as viable for entering the preclinical stage. The Figure's numbers 1-3 correlate to normal phase numbering: the early preclinical stage represents the preclinical, pre-business phase, where the overall net value of the project is negative, the late preclinical stage is at the final phase of the preclinical experiments where the simulated net value becomes positive, the financing rounds 1-3 are equal to the clinical phases 1-3, the 4th financing round represents the regulatory approval, and the last part represents the first year of security monitoring during marketing. The biggest relative value increments take place in the clinical experiment phases 1 and 2; especially when it comes to the final stage of phase 2, the increase in value in euro is substantial.

Figure A5.2 Evolution of market capitalization and ownership stakes in distinctive financing rounds

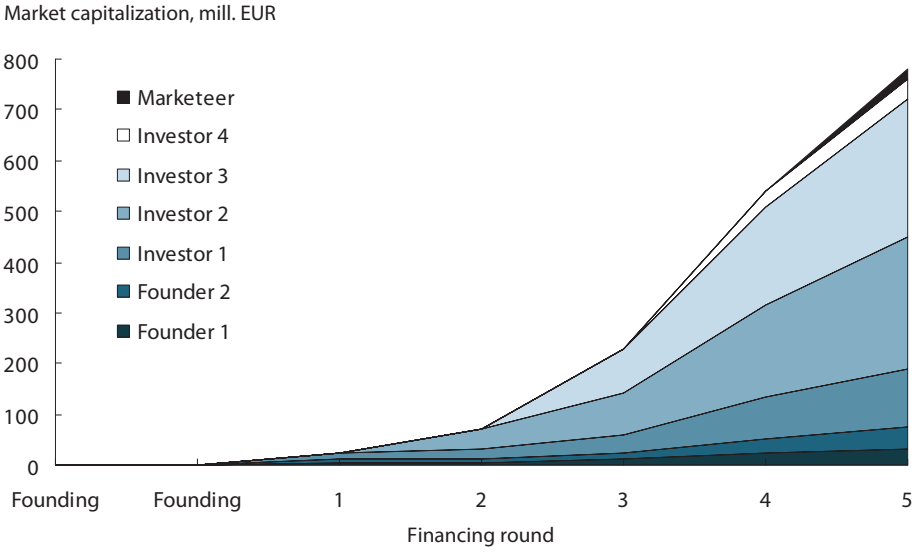


Figure A5.2 is complemented by Table A5.1, which, in addition to the previous, examines the funding needed in each phase, as well as the required [public] subsidies in two different scenarios. In this context the purpose is only to visualize the development of the investments needed, the holdings, and the net value of a successful drug development project. Observe also, that one financier may participate in several financing rounds, and, on the other hand, the presented financial rounds in Figure A5.2 and Table A5.1 may as well be divided into several smaller rounds.

The two lowest rows in Table A5.1 simulate two different extremes in public financing of biopharmaceutical projects: 1) publicly subsidized markets and 2) per-

Table A5.1 Required investments, ownership, and the value increase of earlier investments for each phase in an average simulated drug development project

		Preclinical early stage	Preclinical late stage	Phase 1	Phase 2	Phase 3	Approval phase	Marketing
Founder 1	ownership, %	100.0	43.0	17.0	7.0	4.0	4.0	4.0
	investment, mill. eur	**0.006**	0.12	4.22	5.14	10.1	22.5	31.9
Founder 2	ownership, %		57.0	22.0	9.0	6.0	6.0	6.0
	investment, mill. eur		**0.242**	5.63	6.84	13.4	30.0	42.5
1. Financing round	ownership, %			61.0	26.0	16.0	15.0	15.0
	investment, mill. eur			**15.2**	18.5	36.2	81.1	115.0
2. Financing round	ownership, %				58.0	36.0	34.0	33.0
	investment, mill. eur				**41.7**	81.7	183.0	259.0
3. Financing round	ownership, %					38.0	36.0	35.0
	investment, mill. eur					**86.3**	193.0	273.0
4. Financing round	ownership, %						5.0	5.3
	investment, mill. eur						**29.0**	41.0
Marketer	ownership, %							2.2
	investment, mill. eur							**17.5**
PV: Present value that covers capitalized R&D costs, mill. EUR		0.005	0.423	25.1	72.1	228	539	780
Required subsidy in subsidized markets, mill. EUR		**60.5**	**60.1**	**76.3**	**66.8**	-83.9	-507	-638
Cumulative earnings for entrepreneur at end of project, mill. EUR		**31.9**	**74.4**	**189**	**448**			
Required subsidy in competitive markets, mill. EUR		**9.43**	-45.4	-65.7	-102	-236	-566	-645
Cumulative earnings for entrepreneur at end of project, mill. EUR		**31.9**						

fectly competitive markets. The table will now be analyzed from two perspectives in these subsidy setups: the public financier's and the entrepreneur's.

The government and market structure

Government subsidies are discussed in Chapter 6, where it was concluded that a rational entrepreneur follows the financial pecking order and prefers government subsidies and loans, even over internal financing, as they are risk-free money and do not dilute ownership. Moreover, the financial market can be strongly shaped by the acts of the public financiers.

If the objective is to get one average profitable pharmaceutical development project to enter the market, approximately 10,000 new chemical entities are needed to be screened in the basic research phase. The simulation yields as the risk adjusted value of one such entity to be approximately 5,000 euro, and the expenses to somewhat over 6,000 euro. Consequently, the public sector could provide a general support of 1,000 euro for each new chemical entity -project to be carried out. Such a regular yearly support of a total of 9.4 million euro for one market-entering medicine molecule corresponds to approximately 15% of the annual expenses of the academic bio-engineering research in Finland.

In competitive markets there are many risk-seeking investors willing to finance all projects with a positive NPV. Approximately 250 new chemical entities pass through the final stage of the preclinical phase for each successful drug. The net value of one chemical entity that has passed the preclinical phase is approximately 420,000 euro. Because the research and development costs are approximately 240,000 euro, the business is economically sensible; in this stage the company founder's initial investment of 5,000 euro has risen to a value of 180,000 euro. If the company simultaneously develops two parallel new chemical entities, the growing expenses are compensated for by greater chances of success.

In the scenario of a publicly subsidized market's extreme the government provides subsidies to ensure that the country's pharmaceutical R&D activity will generate at least one drug to the market. In the subsidized market scenario the government subsidies will exceed 260 million euro before the project's NPV becomes positive (lower box in Table A5.1).

The entrepreneur

As discussed earlier, if the company has only one molecule at the beginning of the preclinical phase the chances of success are approximately one in 10,000, and in late preclinical stage the chances of success are one in 250. Because of the low probabilities the net value of the project in the example is only 5,000 euro at the early preclinical stage and slightly over 400,000 euro in the late preclinical stage. In phase 1 the funding need is 15.2 million euro and the [risk adjusted] net value 25 million euro: with an investment of 15 million euro a new investor will get 60% ownership.

The PV row in Table A5.1 represents the net value of the project in each phase, which is also the price for which an investor may buy the whole project. For example in the third financing cycle, equal to the drug development phase 3, a company may invest 86 million euro in the project's development costs and buy the whole ownership from the earlier investors for 140 million euro, thus investing 226 million euro.

An investor at the preclinical stage (the Founder) receives 100% ownership of the project for an initial investment of 6,000 euro. If the Founder remains an owner until the project enters the market, the value of this initial investment increases to more than 30 million euro; this corresponds to 4% holding. Similarly, if the company is established only at the late preclinical stage, the corresponding initial investment of 248,000 euro yields 10% ownership when the project enters the market.

The bottom row in Table A5.1 depicts the increase in wealth for the original entrepreneur when the financial market is highly subsidized. This is to be compared with the respective earnings shown in the box in Table A5.1. It is evident that it is in the strong interest of the Founder to extend full ownership of his or her company as far as possible as his or her total profit in a successful project ($NPV \geq 0$) rises strongly the further he or she can continue without diluting his or her ownership. Consequently, in this simulation the entrepreneur should favor as strong as possible government risk-taking and support. In this scenario the government carries the risks on behalf of private investors, who however fully gain the increase of market capitalization of a succesful product launch.

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CHAPTER 6

THE EFFECT OF TECHNOLOGY SUBSIDIES ON INDUSTRY STRATEGIES AND MARKET STRUCTURE

Raine Hermans – Morton Kamien – Martti Kulvik – Antti-Jussi Tahvanainen

6.1 Introduction

As discussed in Chapters 2 and 4, governments have shown significant interest in promoting biotechnology in general and pharmaceutical applications in particular. Chapter 5 pointed out why a government might want to support the initial stages of drug development that present a negative net present value.

This chapter assesses how implementation of the infant industry argument (IIA) could affect entrepreneurial strategies via injections of government financing. First, how the IIA-based subsidies and financing extend to a conventional financial pecking order is shown theoretically. Then the Finnish biopharmaceutical industry is investigated empirically. The results of this study reveal the framework to be a relevant tool reflecting IIA-based policies in two primary ways: (1) Government *subsidies* become the most highly preferred financial instrument, even more than companies' internal financing and (2) Government *equity financing* is a last resort and a relevant option only for companies with non-market-oriented technology push strategies; in fact, late stage support tends to cultivate lemons instead of market-oriented vital companies, contrary to the original intentions of any government.

6.1.1 Theoretical background

There has been a clear shift towards free trade, concomitant with the development of new technologies that significantly accelerate the transfer of knowledge

and goods. This globalization has forced regions and nations to create the means for restoring and enhancing the competitiveness of their industries: as traditional trade barriers have decreased, other competitiveness-enhancing industrial policies have been created.

In place of trade restrictions, innovative activity has become the central driver of local economic growth (Romer, 1986; Suarez-Villa, 1990; Furman et al., 2002). For example, national innovation systems have been created to stimulate and strengthen dynamic interactions among industrial clusters, universities and public institutions (Porter, 1990; Niosi, 1991; Nelson, 1993; Mowery and Nelson, 1999). The aim of such systems is to support the development and commercialization of new technologies. High technology sectors, often while still in their infancies, are expected to provide new growth opportunities for countries in the midst of global competition.

This article mirrors financing tools based on the infant industry argument to entrepreneurial strategies and the theory of financial pecking order. The infant industry argument, first put forward by List in 1841 (List, 1856), has been used to suggest that government support is a prerequisite for the success of an industrial sector in its infancy because such support dramatically increases the sector's potential for competing favorably with mature foreign industries. Traditionally, the infant industry argument's recommendations were carried out via instruments related to trade policy (see Baldwin, 1969; Krueger and Tuncer, 1982). Yet the more current route to nurturing infant high-technology ventures is through sophisticated instruments related to national innovation policies. For instance, Jensen and Thursby (2001) demonstrate that university patent licensing promotes the industrial applications of government-funded research.

The financial pecking order theory (Myers and Majluf, 1984) involves the explicit assumption that companies have exclusive information on the quality of their operations that external investors lack. This information asymmetry makes financing from external sources more expensive than that generated internally, in the spirit of Akerlof's (1970) seminal paper.

6.1.2 Empirical setup

Finland has been rated one of the top countries in international competitiveness (see e.g. WEF, 2002; WEF, 2003; WEF, 2004; WEF, 2005; WEF, 2006; WEF, 2007; WEF, 2008). The success of the Finnish information and communication technology (ICT) sector has been regarded as evidence of effective policymaking (Rouvinen and Ylä-Anttila, 2003). Because the policy was pivotal to the success of the ICT sector,

it was seen as the key to the success of the Finnish biotechnology sector (Hermans, Kulvik and Ylä-Anttila, 2005).

In Finland much emphasis has been placed on biotechnology research in both academic and industrial settings; thus the number of companies has grown sharply as a result of active innovation policies. However, the domestic pharmaceutical industry has traditionally played only a minor role in Finland compared, for example, to the role of the industry in neighboring Sweden. Therefore, Finland provides a direct empirical example of the modern infant industry argument in action: government bodies support an industrial sector that would otherwise not be capable of successful competition in global markets. The industrial policies have emphasized science-based entrepreneurship and enabled the creation of over a hundred small biotechnology companies within a decade. Overviews of the Finnish biotechnology industry have been provided elsewhere (e.g. Schienstock and Tulkki, 2001; Hermans et al., 2005).

Hall (2002) empirically identifies under-investment, or a "funding gap" related to R&D-intensive business activity, calling for a "further study of government seed capital and subsidy programmes using quasi-experimental methods". To tackle this call, the aim of this study is to assess how an implementation of the infant industry argument on a national level can affect corporate strategies and their capital structure.

The issue is approached by mirroring the strategic orientation of the strongly supported Finnish biopharmaceutical sector against their financing strategy. To that end, the financial pecking order theory was used as the analytical framework. Thus the empirical analysis has two phases: 1. To identify the sources of financing for Finnish biopharmaceutical companies. 2. To investigate whether government financing is related to the strategic orientation and other characteristic features of these companies.

In the first phase sources of financing for and the capital structures of the firms, as well as their market and research orientations, are evaluated. In the second phase, principal component and regression analyses are used to evaluate how sources and types of financing are related to the companies' market- and research-oriented strategies.

The study is organized as follows. Following this introduction, Section 2 provides an overview of the infant industry argument and financial pecking order theory and combines the two frameworks. Section 3 describes the capital structures of Finnish biopharmaceutical companies. Section 4 presents the findings of the empirical analysis and the interconnections between capital structures and strategic orientations of the companies. Finally, in Section 5 the results of the study are discussed.

6.2 Theory

6.2.1 The Infant Industry Argument

Hamilton and List argued that public support could enable a country's infant industry to achieve a leading position over the industries of other nations (List, 1841/1844; List, 1856); for a comprehensive summary see Shafaeddin, 2000). The infant industry argument (IIA) is based on the temporary need for protection (or support) of an infant industry, if the industry is unable to grow in the context of free trade and foreign rivals. The initially high costs of providing industry support are assumed to be compensated for *via* learning by doing of the industry, thus stimulating excessive profits and economic growth in subsequent stages (Bardhan, 1971). The IIA states that this growth might not have been captured without short-term government support However, the IIA is sometimes tempted to be utilized as justification for exceedingly long-term protection, contrary to List's original view.

One rationale for supporting an infant industry is that it stimulates cumulative learning within the sector through the creation of positive externalities over time. Such Marshallian type (Marshall, 1920; Krugman, 1991) externalities include, for example, the availability of technically competent labor, technological spillovers, and diminishing transport costs of intermediate inputs due to the creation of a local cluster. If these externalities could only be created through government promotion, and if the long-term GDP gains exceeded the initial short-term costs of the promotion, it would be reasonable to provide temporary support for the infant industry. Thus the IIA diverges from static trade restriction schemes, which protect domestic industry through permanent import tariffs, quotas, or similar means.

There are several modern versions of the conventional IIA. Although there is increasing consensus on the need for free trade, many developed and less-developed regions execute industrial programs, for instance, in the name of developing their national innovation systems or of encouraging entrepreneurial ventures. Jensen and Thursby (2001) state that the original inventor should be provided clear economic incentives by the academic institution controlling the intellectual property rights to the invention, as otherwise the relationship between the inventor and the university would lead to a conflict of interests and a potential moral hazard problem discouraging innovation activities.

Jensen's and Thursby's statement is also compatible with the most recent interpretation of the IIA: broadly available and relatively inexpensive government services and financing strengthen the industrial base for the latest and most promising industrial branches, such as the business sector based on biotechnologi-

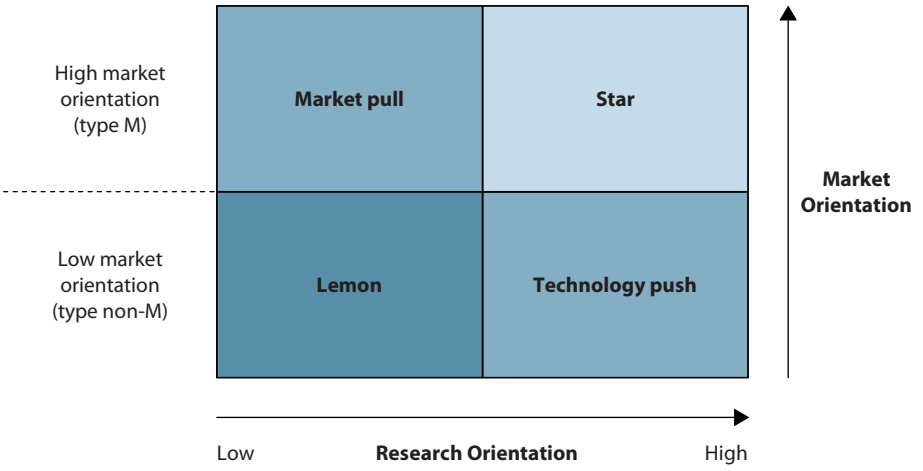
cal innovations. Here the infant industry argument is utilized and how companies that have received government financing differ from firms with funding from other sources is investigated.

6.2.2 The capital structure literature

There is a vast literature related to capital structure. The capital structure literature mainly analyzes the rationale behind companies' choices of distinctive forms of financing. This study utilizes the pecking order hypothesis presented by Myers and Majluf (1984) and Myers (1984). Harris and Raviv (1990) and Klein et al. (2002) draw a more comprehensive picture of theoretical perspectives on capital structure choices.

Myers and Majluf (1984) analyze information asymmetry between entrepreneurs and external investors. Information asymmetries may decrease the expressed value of a company. The depreciation may even lead to a rejection of positive net present value (NPV) development projects. Asymmetric information could also provide an incentive for moral hazard behavior. A simplified example is provided below.

Figure 6.1 Definition of strategic orientations



Source: Kamien and Schwarz (1982).

High-technology companies can be divided based on their market and research orientations, respectively. In this classification, corporate strategies, based on the companies' market and research orientations, are divided into star, market-pull, technology-push, and lemon categories, respectively (Figure 6.1).

The companies are divided into two categories of market orientation: those with a market-oriented strategy (**M**), and those with a reasearch-oriented strategy (**non-M**). Both companies can be technologically advanced and stable. Market-oriented companies have a clear strategic aim towards a market place, whereas the research-oriented companies rely on competencies other than the explicit ability to capture the commercial value of their technology. Due to information asymmetries investors are unable to determine whether the target company is of type **M** or **non-M**. This is the starting point for this illustration of the financial pecking order theory as well as for the data analysis.

The financial pecking order theory

Both types of companies, M and non-M, may have a development project that could be realized using external financing by issuing new equity. As investors are unable to distinguish M from non-M companies, they face a haphazard risk: if they value the company as type M, but the company turns out to be type non-M, they would overvalue the company and pay too much for the new equity. This would provide supernormal pay-offs to the current owners of the company, and the managers of the non-M type company would have no incentive to identify their firm as non-M because they aim to maximize the wealth of their current owners.

Anticipating this behavior and an inability to valuate the company, the investor would adjust the overall valuation scheme in order to control for these risks: all companies' equity would be priced to a level corresponding to the non-M value, and hence below the fair value for an M firm.

Managers of the M type company would find the situation somewhat contradictory. The current owners of the M company would have to consider whether their net wealth gain still remained positive. If the wealth loss of the current owners did not exceed the overall NPV of the development project, the project should be accepted in economic terms. However, the project could be rejected, even if it had a positive NPV, if the projected wealth decrease of the current owners of the M company exceeded the project's NPV.

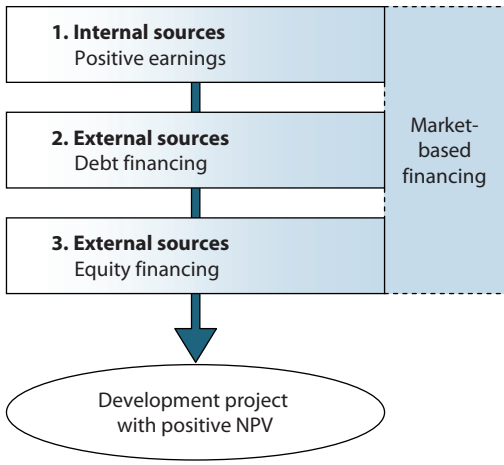
The asymmetric information approach implies that an M type company would issue equity only if it had no other project-financing option. In contrast, non-M type companies would have nothing to lose, which would make equity financing

an appropriate instrument for them. Based on this reasoning, by issuing new equity, the company signals that it is type non-M.

Consequently, companies follow a financial pecking order as described by Myers and Majluf (1984) (Figure 6.2):

1. The company exploits its internal sources of financing: company revenues, or equity issuance for insiders. Because information asymmetry does not occur among insiders, there will be no wealth losses and equity would not be undervalued. Furthermore, there will be no issue fees or trade costs associated with the internal financing, which implies that it would be economically superior to any other source of financing. Only in cases where no internal financing was available for all the development project(s) with positive NPV would other financial sources be used.
2. Companies prefer debt financing to equity financing because the debt interest is usually tax-deductible and the single bond security is a fixed claim with the same value independent of the type of company. Thus, debt financing is cheaper than equity financing for a type M company and even for a non-M company when issuing equity is more costly than issuing debt.

Figure 6.2 The pecking order of market-based financing at any stage of the company's life cycle



Source: Myers and Majluf (1984).

3. External equity financing is used as a last resort to finance promising development projects, due to the dilution effects mentioned above.

The company makes a new assessment and financing choice for each new NPV project. Typically a well-established company has a real choice among financial instruments as it can have retained earnings, as well as collaterals for a possible loan. For a young company the true choices are very limited. However, the financial pecking order *preferred* by all companies remains the same across situations.

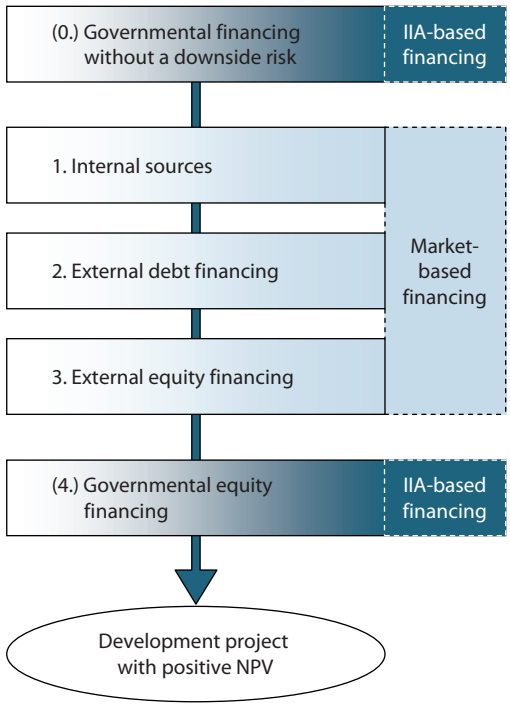
Financing based on the infant industry argument: an extended financial pecking order

The introduction of financial instruments in concordance with the infant industry argument necessitates an extension of the concepts of the original financial pecking order theory (Figure 6.3). If the government loosens the terms of financing, a company's management might prefer government financing to any other financial source in order to minimize the efforts and risks related to the financing. This is the case especially if the loans do not require repayment in the case of project failure. In this case the loans can be viewed as a virtually risk-free source of financing for a company. Such government funding would thus transcend the conventional pecking order to become the first choice for companies.

Government financing organizations specializing in venture capital type financing have an inherent principal-agent problem. The government venture capitalists are by definition not true venture capitalist entrepreneurs as they operate with outside (*i.e.* taxpayers') money, and hence are virtually free from downside risks caused by internal and external factors. Moreover, an upside resulting from successful government investment is not reflected primarily in the wealth of the responsible investment managers. Consequently, government venture capitalists may not have explicit incentives to pursue results in the best interests of the financier or the original owner of the company. A second problem is connected to the political principals of a government venture capital organization: even if the government venture capitalist provides the same conditions as its private counterpart, there might be a risk of arbitrary decision-making due to changing political climates.

Both the principal-agent problem and the "political risk" should guide the financing provided by a government venture capitalist in the opposite direction of the pecking order than government subsidies. Government equity financing becomes even less preferred and more expensive than equity financing obtained from a private venture capitalist. Consequently, if a company has a strong injec-

Figure 6.3 Infant industry argument (IIA) extends beyond the financial pecking order at any stage of the company's life cycle



Source: Adapted from Myers and Majluf (1984) and List (1841/1844).

tion of government venture capital, it might have a negative signaling effect in the following rounds of financing.

6.3 Data and empirical setting

6.3.1 Characteristics of empirical data

The data used in this study are derived from a database compiled by ETLA, The Research Institute of the Finnish Economy, covering financial and business-related information on 84 companies operating in the biotechnology sector. 42 small and medium-sized firms that indicated they are part of the pharmaceutical industry or

that their clients or subcontractors are in the pharmaceutical industry were selected from the database. ETLA's biotechnology company database was collected in 2002-2004. Hermans and Luukkonen (2002) and Hermans et al. (2005) present a detailed description of the data. The information from financial statements has been cross-checked with the trade register of the National Board of Patents and Registration of Finland. A comparison of Finnish biopharmaceutical small and medium sized enterprises to all SMEs[1] is presented in Table 6.1. The number of employees in biopharmaceutical SMEs is relatively high when compared to other Finnish SMEs as a whole, but their sales revenues are lower on average than those of companies in other industries. Despite the fairly high number of employees, 45% of the companies show a turnover of less than 200,000 euro, compared to only 15% of other SMEs. The biopharmaceutical sector's sales are oriented more toward foreign markets than sales of all companies on average and the companies are comparatively young. Slightly more than a third of the biotechnology companies were founded in 1997 or afterwards, while the corresponding proportion for all SMEs is 14%.

The biopharmaceutical sector's emphasis on scientific research is evident from examining the companies' outlays on research and development (R&D) as a percentage of their total expenses. Accordingly, 75% of the biopharmaceutical companies have patents or patents pending, while 94% of all Finnish SMES have neither of these.

R&D activity is typically associated with expectations of future revenues. However, this emphasis on future commercialization increases business risks, which will in turn elevate the yield requirements of investors. Given the revenue expectations of entrepreneurs and the yield requirements of investors, it is understandable that 86% of the biopharmaceutical companies in the sample expect their turnover to rise over the next five years at an average annual rate exceeding 10%, compared to only about 20% of all SMEs.

[1] Below we use the term SMEs to denote small and medium-sized enterprises. A company is called small or medium-sized if two of the following three conditions are met: the company has a maximum of 250 employees, its turnover does not exceed EUR 40 million and its total assets are less than EUR 27 million.

Table 6.1 Comparison of Finnish Biopharmaceutical SMEs and SMEs as a whole

	Bio-pharmaceutrical SMEs, %	Total SMEs, %[2]
Number of employees		
< 5	33	44
5-20	38	41
> 20	29	15
Turnover, million euro		
< 0.2	45	15
0.2-1.5	40	56
1.6-8.0	12	24
> 8	2	5
Exports/turnover		
0 %	43	70
0-1 %	2	22
2-5 %	7	4
6-10 %	0	2
> 10 %	45	3
Unknown	2	0
Age of company, years		
0-2	14	5
3-4	21	9
5-24	64	70
>24	0	16
R&D expenditures/total costs (total SMEs = R&D expenditures/turnover)		
0 %	5	53
0-1 %	2	23
2-5 %	5	13
6-10 %	7	3
> 10 %	79	6
Unknown	2	0
Company has patents or patent applications		
Yes	74	6
No	26	94
Company's expected turnovergrowth over next 5 years (total SMEs = next 3 years)		
< 0 %	0	1
0-1 %	2	31
2-5 %	0	20
6-10 %	10	23
> 10 %	86	21
Unknown	2	5
Total observations in sample	***42***	***754***

Source: Trade register of the National Board of Patents and Registration of Finland, Hermans and Luukkonen (2002), Hermans, Kulvik and Tahvanainen (2005) and authors' calculations.

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[2] Hyytinen and Pajarinen (2003) used sector-specific data on Finnish companies to uncover the real structure of Finnish SMEs. This study weighted the data according to the age of the companies, as in Hermans and Kulvik 2005). The weights are obtained as follows:

$\frac{n_{total(t)}}{n_{sample(t)}}$. The term n denotes the number of companies in the total population and the sample. Term t denotes the three groups (t=1,2,3) in order of age. Group 1, group 2 and group 3 consist of companies founded in 1997-2001, 1991-1996, and earlier, respectively.

6.3.2 Capital structure and financial sources

Types of capital

This section investigates the financing received by biopharmaceutical companies, broken down by type of capital. The empirical handling of capital structures was influenced by a study on the SME sector in the US (Berger and Udell, 1998), a study on the capital structure of Finnish small and medium-sized companies (Hyytinen and Pajarinen, 2003), and a study of capital structures in the biotechnology industry (Tahvanainen and Hermans, 2005).[3]

Equity and capital loans are prominent forms of financing in all biopharmaceutical companies in the sample (Table 6.2). Equity and capital loans are considered part of the total shareholders' equity. Capital loans are a specific version of financing offered by government institutions in Finland. A company pays interest on capital loans only if it has profits to pay out.

The capital loans supplied to biopharmaceutical companies have come almost entirely from the public sector, with the National Technology Agency of Finland (Tekes) accounting for over 80% and the Finnish National Fund for Resarch and Development (Sitra) for 15% of the total amount. The role of Sitra as a source of capital loans is especially pronounced in small companies with less than 20 employees.

Table 6.2 Capital structure by age and size of biopharmaceutical companies

	Equity, %	Capital loans, %	Loans, %	Total financing (million euro)
Total	70.6	18.3	11.1	225.4
0-4 years	77.1	10.5	12.4	134.9
5-8 years	71.0	27.9	1.1	59.3
9-24 years	41.4	33.6	25.0	31.2
Small	49.9	36.5	13.7	20.6
Large	72.6	16.5	10.9	204.8

Source: *ibid*.

[3] Because almost half of the companies showed a loss in the fiscal period evaluated, the realized losses reduced the amount of equity on the balance sheet. Because we want to assess how much has been invested in the companies in the form of equity and capital loans, the realized losses are not taken into account in our study. Thus, the total equity presented in Table 2 does not correspond to the figures obtainable directly from the balance sheets.

As biopharmaceutical companies' assets are mainly based on intangible assets and competencies, they – especially younger companies – seldom have collateral with which to secure loans. Consequently, loans account for 11% of total financing on average. Thus, only older companies with stabilized operations and accumulated tangible assets have traditional bank loans.

Loans provided by Tekes can be given without major collateral and do not require repayment if the financed project fails. Thus the loans provide virtually risk-free project-financing and are highly preferred by companies. Due to the repayment terms, investigators should not consider such financing an ordinary loan, as Tahvanainen and Hermans (2005) did, but more of a subsidy.

The total equity financing of SMEs operating in the pharmaceutical industry is estimated to be slightly less than 160 million euro. The major owners of the companies are actively engaged in the business, private venture capital companies, and government institutions providing venture capital, mainly Sitra. The nominal value of the equity financing of older firms is less than that of their younger counterparts at the end of 2001. This may be explained by inflation and by smaller levels of initial investments particularly in those matured companies that can generate sales and positive profits.

Especially in older companies the owners are likely to be non-financial companies; other companies own over 60% of the shares of biopharmaceutical companies more than 8 years old, whereas private venture capital companies and government institutions have proportionately greater ownership of younger companies.

Capital structure related to companies' financial performance

Most of the equity financing is focused on firms with turnover less than 1.5 million euro (Table 6.3). Those few companies that have succeeded in generating higher sales are mostly owned by non-financial companies. These companies primarily export their products or services.

The time from innovation of a drug to the final product launch may take 10 to 15 years (DiMasi et al., 2003). Hence, a start-up firm's R&D activities and intangible assets are of pivotal importance when assessing the firm's present value from its expected stream of revenues (e.g. Garner et al., 2002). The companies' high levels of R&D activity might reflect the investors' emphasis on the importance of R&D activity as a way of boosting future revenues, or the activity may signal future revenue expectations to investors, making the company a more attractive investment target (Table 6.3, High R&D intensity).

Table 6.3 Equity financing by realized turnover (i.e. sales revenue) and export intensity of biopharmaceutical companies

	People active in the business, %	Other people, %	Private venture capital company, %	Other financial institution, %	Other company, %	Government institution, %	Other, %	Total share financing, mill. euro
Turnover under 1.5 million euro	26.3	5.1	33.6	2.6	5.9	25.0	1.4	147.6
Turnover over 1.5 million euro	16.8	0.6	7.4	2.3	67.4	5.5	0.1	11.5
Low R&D intensity	4.5	0.2	0.0	0.0	93.8	1.5	0.0	7.5
High R&D intensity	26.6	5.0	33.3	2.7	6.2	24.7	1.4	151.6

Source: *ibid*.

In Table 6.4 the ownership structure is broken down by the sales expectations indicated by the company, with the threshold of a company's own expectation of its sales after 5 years set at 1.5 million euro. People actively engaged in the business own about 25% of the companies with both low and high revenue expectations.

Table 6.4 Equity financing of biopharmaceutical companies by expected turnover in 2006 and expected annual growth in turnover

	People active in the business, %	Other people, %	Private venture capital company, %	Other financial institution, %	Other company, %	Government institution, %	Other, %	Total share financing, mill. euro
Expected sales in five years below 1.5 million euro	26.4	6.4	36.1	3.3	0.1	27.4	0.2	107.4
Expected sales in five years above 1.5 million euro	23.9	1.4	22.6	1.1	31.6	15.9	3.5	51.7
Expected rate of growth less than 25% per annum	24.1	4.5	38.6	0.3	8.7	23.5	0.3	90.3
Expected rate of growth greater than 25% per annum	27.6	5.2	22.8	5.6	12.5	23.8	2.6	68.7

Source: *ibid*.

Private venture capital firms own on average slightly over a third of companies with revenues anticipated to remain below 1.5 million euro over the next five years, but they account for slightly over 20% of the ownership of companies with higher revenue expectations over the same time. The role of government sources of venture capital, especially Sitra, is high in companies whose turnover is not expected to surpass 1.5 billion by 2006. On the other hand, non-financial companies have invested almost exclusively in companies whose sales expectations are relatively high.

In this section the capital structure of companies in the biopharmaceutical sector have been presented, broken down by characteristics of the biopharmaceutical companies. In the next section a more systematic overview of the above-described capital and ownership structures are presented using statistical means.

6.3.3 Indicator construction

Market orientation of the companies

Six indicators are used to characterize the market-orientation of the companies. Descriptive statistics for the 6 market-orientation variables are presented in Table 6.5.

The first variable represents current value creation by the company, as measured by annual revenues. The second indicator relates to future value creation expectations, estimated by anticipated annual revenues five years after the time of survey. These estimates may include some upward bias because they are disclosed by the companies themselves and thus tend toward more optimistic outcomes. However, the anticipated sales seem to be related closely to the company's actual level of intellectual capital, the foundation for future earnings as demonstrated by Hermans and Kauranen (2005). For the current purposes, the measure was simplified and a dummy created indicating whether the anticipated future sales are above 8 million euro (1) or not (0).

The third indicator of market-orientation, exports intensity, approximates an orientation towards the globalized markets of pharmaceuticals. This indicator is estimated as the exports' share of the total revenues of the company. Such a measure is especially relevant in this study's context: a small open economy of which domestic markets constitute a vanishing share of the global markets.

The fourth indicator, customer dependence, is a dummy variable based on whether the company has a principal customer whose purchases exceed 33% of the company's annual revenues. This indicator provides important information on the company's customer relations as a part of its market orientation.

Table 6.5 Variables indicating market-orientation

Direct market orientation	N	Minimum	Maximum	Mean	Std. Deviation
Current value creation (turnover in million euro)	42	0.00	27.53	1.27	4.28
Future value creation (turnover in 5 years)	41	0.00	204.46	12.21	35.42
Export intensity (export/sales <=10%=0 >10%=1)	41	0.00	1.00	0.46	0.50
Customer dependence (principal customer (>1/3))	42	0.00	1.00	0.43	0.50
Managerial experience (manager's business experience in years)	42	1.00	40.00	10.60	8.42
Auditing expertise (top 5 auditor)	42	0.00	1.00	0.71	0.46

Source: *ibid*.

The fifth indicator for market orientation approximates the company's business and management experience, as measured by how many years a chief executive officer (CEO) has been active in managing businesses.

The last indicator is based on whether or not the company has retained the services of one of the five largest international auditing companies. This might relate to the company's reliability in the eyes of potential international business partners.

Research orientation of the companies

Research activity is the heart of any business in the field of drug discovery. The initial research leading to an innovation may be conducted within academia or a company. 74% of the biopharmaceutical companies within the data set state that their origin stems from an academic biotechnical research idea, and 19% of the companies are spin-offs of other companies. Thus, the industry as a whole can be expected to be extremely research-oriented, with business based almost entirely on R&D activity. Table 6.6 lists four variables used as indicators of company research orientation.

The first indicator estimates the research intensity as a ratio of R&D costs to total costs of the company. If the ratio is close to 100%, it means that the company has no in-house sales activity: it either has no sales or has out-licensed its distri-

Table 6.6 Variables indicating research-orientation

Research orientation	N	Minimum	Maximum	Mean	Std. Deviation
Research intensity (R&D costs per total costs, %)	42	0 %	100 %	51 %	0.36
Education intensity (Share of employees holding PhD degree out of total labor, %)	42	0 %	100 %	35 %	0.31
Research productivity (patent applications + patents/labor)	42	0.00	21.43	2.06	4.45
Research collaboration (collaboration with foreign academic institutions, %)	42	0 %	100 %	26 %	0.45

Source: *ibid*.

bution efforts. In both cases, the company's research intensity remains the main driver of value creation.

The second indicator measures formal research education intensity of employees as the ratio of the number of employees holding a PhD degree to the total number of employees.

The third indicator relates to research productivity in terms of intellectual property rights as output from R&D activity (Suarez-Villa, 1990; Furman et al., 2002). This indicator is measured as the ratio of number of patent applications and patents to the number of total number of employees. The size of the patent portfolio is often related directly to earnings prospects, especially in a high-tech industry such as drug development (Hermans and Kauranen, 2005). However, the number of approved patents will usually be substantially lower than the number of patent applications. As pharmaceutical companies are assessed in part based on their relatively high number of approved patents, small biotechnology companies will also attempt to produce a significant patent portfolio (Nikulainen et al., 2006). Thus, their patent portfolio becomes biased towards patent applications. The conclusion is that using the number of patent applications as an indicator of research productivity provides a valid proxy for research orientation of the biopharmaceutical company.

The fourth indicator for research orientation describes international academic collaboration as measured by a dummy variable based on whether the company collaborates with a foreign academic institution (1) or not (0). A reflection of the very unique research-oriented nature of the industry is that 95% of the companies collaborate at least with one domestic academic institution and 26% with at least one foreign institution.

Table 6.7 Control Variables indicating size, age, and location of companies

Controls	N	Minimum	Maximum	Mean	Std. Deviation
Size (employees)	42	1	82	16.5	19.2
Matureness (age of firm)	42	0	21	6.69	4.47
Hub location (in Helsinki, %)	42	0 %	100 %	36 %	0.48
Hub location (in Turku, %)	42	0 %	100 %	36 %	0.48

Source: *ibid*.

Four control variables were used in the empirical analysis to detect any potential effects or correlations specific to size, age, or location of the companies (Table 6.6). Company size is estimated by the total number of employees, maturity is measured by the age of the company, and two dummy variables represent location: Helsinki and the Turku region each house 36% of the biopharmaceutical companies in the sample, and the location dummies reveal whether distinctive investor groups demonstrate any geographic preferences.

6.4 Empirical models

The empirical analysis was conducted in two stages. First, the depth of market and research orientation of the companies was described and measured, and then these measures were related to the sources of financing. In The second stage estimated how the market and research orientations of the companies are configured when they are financed by distinctive government and private sources of financing using a logistic regression model. The results of the regression analysis reveal the interaction, if any, among the strategic orientations of the companies, the infant industry argument and the modified pecking order hypotheses related to the biopharmaceutical business.

The first stage compresses the information hidden in the overall and partial co-variations within the initial data to form uncorrelated linear combinations of the observed variables. It was possible to identify between-variable groups of loadings representing distinctive indicators of the market orientation and research orientation of the companies. Some companies might be leaning on exceptionally high current R&D expenses in order to create abnormally high future earnings. This would be expressed both as research and market orientation in a single principal

component. More generally, the principal component loadings provide information on how market-orientation and research-orientation of the companies interact within the data set.

The results of the first stage of analysis provide solid grounding for the second stage analyses: the resultant principal component scores are used as independent variables in the regression model. Using principal component scores in place of the original individual variables reduces risks for multi-collinearity of the independent variables within the model because the principal components measure co-variation of the initial variables but are uncorrelated to one another.

6.4.1 Results from the first stage: principal components and strategic orientations

Principal components were formed to assess the different strategic orientations of the biopharmaceutical companies within the sample. The varimax rotation method simplified the interpretation of the principal components by minimizing the number of initial variables that correlate with any principal component. The method seeks to produce a rotated final result where each variable is prominent in only one principal component.[4] The rotated principal components analyzed explain slightly over half of the variance of the selected variables. The principal components are distinguished according to whether the correlation between the selected variable and the principal component is over 0.3, which corresponds roughly to the correlation level that differs significantly from zero, taking into account the sample size and assuming a normally distributed population. Six principal components, the eigenvalues of which are greater than 1, are named.

This method produced six principal components with eigenvalues greater than 1. The resulting components all represent a certain composition of strategic orientations. The rotated principal components are shown in Table 6.8. To assess the companies' strategic orientations, the components were divided into type M (market-oriented strategy) and type non-M (non-market oriented strategy) using the strategy matrix described earlier.

Component 1, "Established business": This reflects an ongoing business strategy; the CEO is experienced, the company protects its intellectual property by patents, has established solid export channels, and shows high current sales. This is a type **M**

[4] Sharma (1996), for example, provides a detailed technical presentation of principal component analysis.

Table 6.8 Principal components depicting strategic orientations within the biopharmaceutical business

Rotated component matrix [a]	Component 1	2	3	4	5	6
Ln age (Control)	**0.801**	-0.025	0.068	-0.135	0.023	0.065
Export/sales >10% (**M**)	**0.707**	*-0.320*	0.167	-0.103	-0.294	0.045
Patents per labor (**non-M**)	**0.632**	**0.336**	-0.180	0.189	0.037	-0.203
Principal customer (**M**)	0.115	*-0.807*	0.047	0.239	0.106	0.262
Collaboration with foreign academic institutions (**non-M**)	0.083	**0.681**	0.262	0.173	-0.087	0.082
Anticipated sales >8meur (**M**)	0.008	0.156	**0.848**	-0.160	0.025	0.090
Ln revenues (**M**)	**0.443**	-0.275	**0.583**	-0.111	0.114	*-0.388*
Ln employees (Control)	-0.042	**0.527**	**0.554**	0.001	-0.225	0.212
Turku (Control)	-0.097	0.154	-0.097	**0.882**	0.151	-0.052
Helsinki (Control)	0.039	0.204	0.150	*-0.829*	**0.306**	0.058
Top 5 auditor (**M**)	0.106	0.291	0.013	0.125	*-0.811*	0.153
Ln CEO's business experience (**M**)	**0.495**	0.268	0.202	-0.083	**0.564**	0.284
PhDs per total labor (**non-M**)	-0.095	-0.111	*-0.428*	0.119	**0.477**	0.124
R&D costs per total costs (**non-M**)	0.015	-0.085	0.034	-0.094	0.003	**0.913**

Extraction method: principal component analysis.
Rotation method: varimax with Kaiser normalization.
M = market oriented strategy.
non-M = non-market oriented strategy.
[a] Rotation converged in 16 iterations.

Source: *ibid*.

strategy, showing high scores for both market and research orientation. According to this study's classification, companies showing such a strategy are Potential Stars. The reversed component 1 is an "Infant stage" strategy revealed by companies lacking an experienced CEO, international market relations, a patent portfolio, and current sales. This strategy is associated with Lemon companies of type **non-M**.

Component 2, "International scientific collaboration": This strategy lacks exports and a principal customer, but has established foreign academic collaboration, a critical mass of employees and many in-house patents. This is a type **non-M**, Research Oriented Strategy. The reversed component 2 strategy in this study is called "Foreign customer focus", a type **M**, Market Oriented Strategy.

Component 3, "Sales Orientation": This describes a strategy that has led to high current sales along with high anticipated future sales, and a significant critical mass of employees, but a relatively low number of PhDs. This is a type **M**, Market

Oriented Strategy. The reversed component 3, "Scientific competence" strategy is associated with no present nor anticipated future sales and few employees, but a relatively high number of PhDs. This is a purely Research Oriented Strategy of type **non-M**.

Component 4, "Location in Turku": This component has a reversed component, "Location in Helsinki". The locations were control variables, and the result suggests that corporate strategies do not vary according to company location. Consequently, this component cannot be placed in any specific category of this classification.

Component 5, "Human resources": This is a type **M** strategy showing both a market and research orientation. The strategy includes both a high ratio of PhDs to total employees, as well as a CEO with significant business experience. Moreover, it is located in Helsinki. According to this classification, this should be a Potential Star. Strategies characterized by a reversed component 5 comprise a Top 5 auditor but lack internal human resources, and this strategy is called "External control", and as such it is a Lemon strategy within this classification.

Component 6, "R&D": Strategies associated with this component show a high R&D intensity but low current sales. This is clearly a Research Oriented Strategy of type **non-M**. The reversed component 6 is associated with a low R&D intensity but high current sales, and is consequently named "Sales", a Market Oriented Strategy of type **M**.

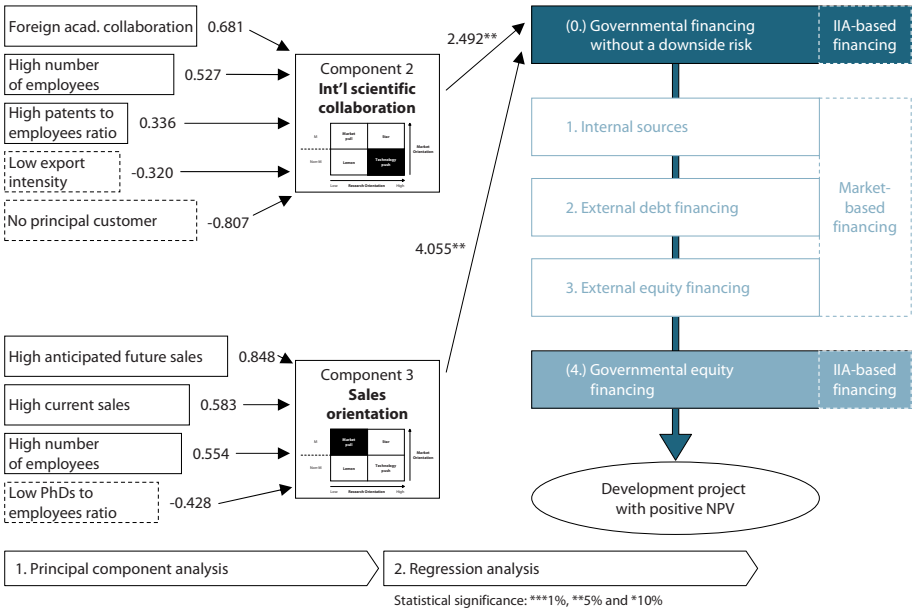
6.4.2 Second stage results: logistic regression analysis

A standard logistic regression model is utilized to reveal the types of strategic orientation with which companies at each stage of the extended financial pecking order framework are associated. The dependent variables are dummies indicating whether the company has received financing from a financial source related to a specific stage of the pecking order. The logit regression model is of the following form:

$$\text{logit } P_t = \alpha_i + \beta_i X + \varepsilon_i, \tag{6.1}$$

where the left hand of Equation 6.1 depicts the odds ratio of a probability (P) to obtain funds from the i^{th} source of financing. Term α is a regression constant. The vector X represents the principal components derived in the analysis above, and the regression coefficient of the vector X is denoted by β, measuring to what degree the strategies revealed by principal components can be related to financing from the i^{th} source (the results are presented also in Appendix 6.2 in table format).

Figure 6.4 The strategic orientations of companies receiving government subsidies and loans as part of IIA policies



Government financing without a downside

Government financing without a downside refers to risk-free subsidies and loans provided by Tekes. 96% of the companies applied for such direct or indirect subsidies, with 65% of the companies ultimately receiving this financing from Tekes. Consequently, the strategic orientations depicted in Figure 6.4 mainly reflect the selection criteria of Tekes. The company profiles show both market-driven and research-oriented strategies (Figure 6.4). As the majority of companies have received 0-type government financing risk-free, the logistic regression results suggests that it is sufficient to show either of the following to receive Tekes funding:

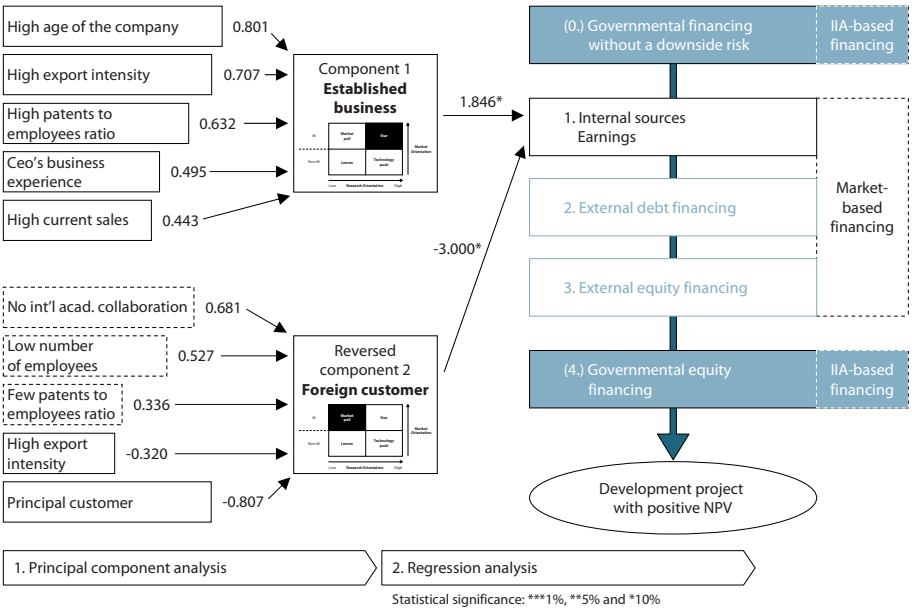
1. A large international research network (see Kamien and Tauman (2002) for a deeper comparison of the most profitable modes of licensing by an inventor who is an industry incumbent with one who is an outsider).
2. High sales, either disclosed by the company itself as high anticipated future sales, and/or high present sales.

This leads to the conclusion that the strategic orientations of the preferred companies can be either type **M** or type **non-M**.

Internal sources: earnings

Market-based internal financial sources are clearly related to a type **M** corporate strategy. As Finland is a small open economy, high current sales typically relate to a high export intensity. Moreover, success in international markets seems to be associated with a higher age or later stage of the company or, in the case of a younger company, with the establishment of a strong relationship with a foreign principal customer (Figure 6.5). Himmelberg and Petersen (1994) show that internal sources are a significant form of R&D financing for publicly listed companies in the USA.

Figure 6.5 The strategic orientations of companies generating positive earnings



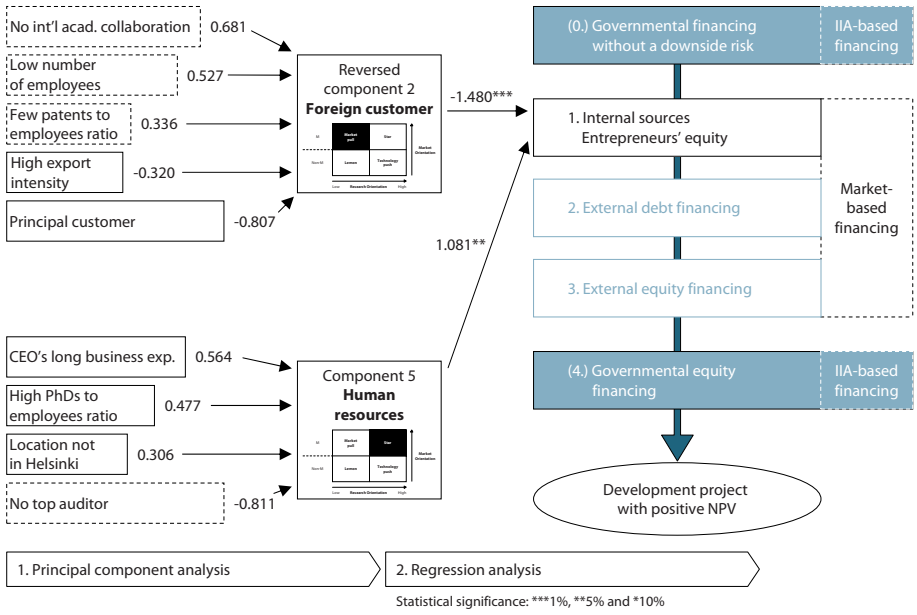
Internal sources: entrepreneurs

The term "entrepreneurs' equity" refers to ownership of more than 50% of the shares of the company by individuals who are active in the company's business. These employee-driven companies seem to implement clear internationally oriented strategies, having based their niche and combination of market and research

orientation on the business experience and scientific knowledge of their employees (Figure 6.6). Moreover, the companies show high dependence on single foreign customers – equal to that of the companies with internal sources of financing stemming from earnings – thus warranting their status as having a type **M** corporate strategy. However, even though this dependence on a single customer may provide some stability of cash inflows, the loss of such a customer may be insurmountable for a small enterprise.

The market orientation of these entrepreneur-driven companies is parallel with the findings of the literature assessing agency costs. Agency costs reflect the costs of shareholders to monitor manager's behaviour and decision-making, and consequently agency costs are zero if the manager owns 100% of the equity. In the entrepreneur-driven companies managers own at least one half of the equity, which seems to lower agency costs in terms of market orientation (e.g. Ang et al., 2000).

Figure 6.6 The strategic orientations of companies with entrepreneurial ownership and financing

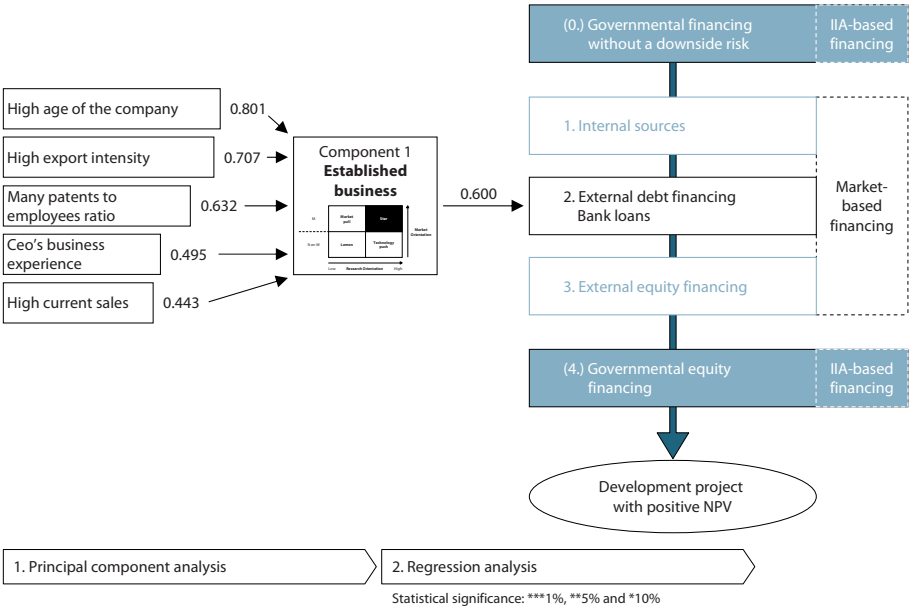


External debt: bank loans

In this study the bank loans consisted of only 2.5 million euro, and thus formed only a minimal portion of the total financing. This is likely the reason no strategic orientation was able to characterize this financing entity. However, Component 1, "*Smooth business*", predicted most significantly ($p<.25$) the reception of bank loans (Figure 6.7). This suggests that older and more proven type **M** companies had been able to attain debt financing.

No significant relation was found between strategic orientations of the companies and the external debt financing provided by banks. Bhagat and Welch (1995) argue that this relationship depends on cultural context: R&D activity seems to be financed by debt rarely among U.S. firms, but more often in Japan.

Figure 6.7 The strategic orientations of companies receiving bank loans



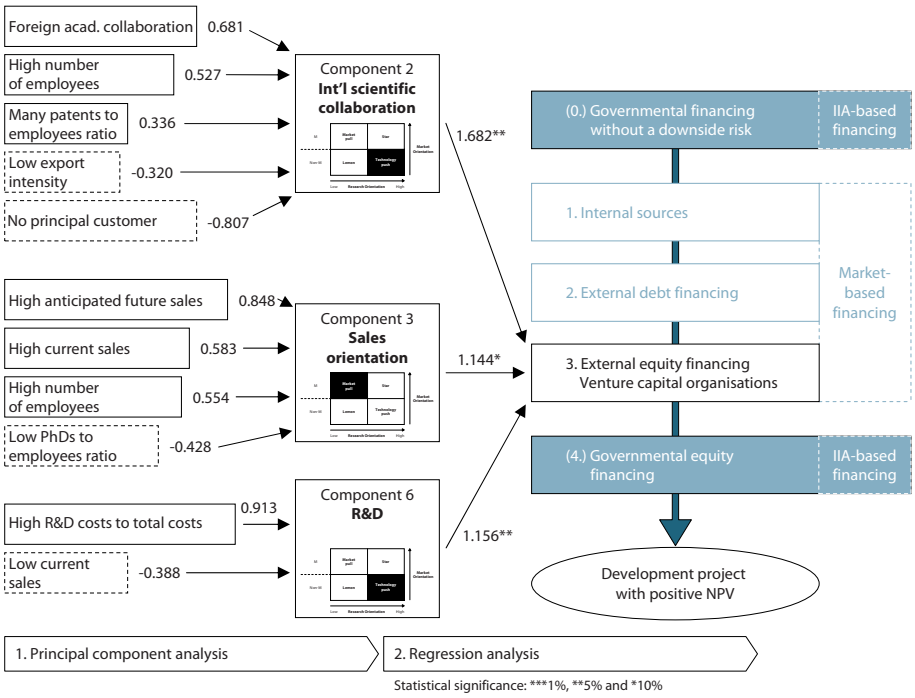
External equity financing: venture capital organizations

Companies that have been unable to obtain financing from earlier-stage sources in the pecking order generally seek external equity financing for their positive NPV projects. The probability of receiving financing from venture capital companies is higher when the firm shows any combination of the following strategic orientations (Figure 6.8):

- International scientific collaboration (**type non-M**)
- Sales orientation (**type M**).
- Intensive R&D activity (**type non-M**)

The simultaneous appearance of high current sales in component 3 and low current sales in component 6 is in line with the findings of Hermans and Kauranen (2005), where high anticipated future sales were not related to the current sales of the company but instead to a large patent portfolio, intensive R&D activity, uni-

Figure 6.8 The strategic orientations of companies receiving equity financing from venture capital companies



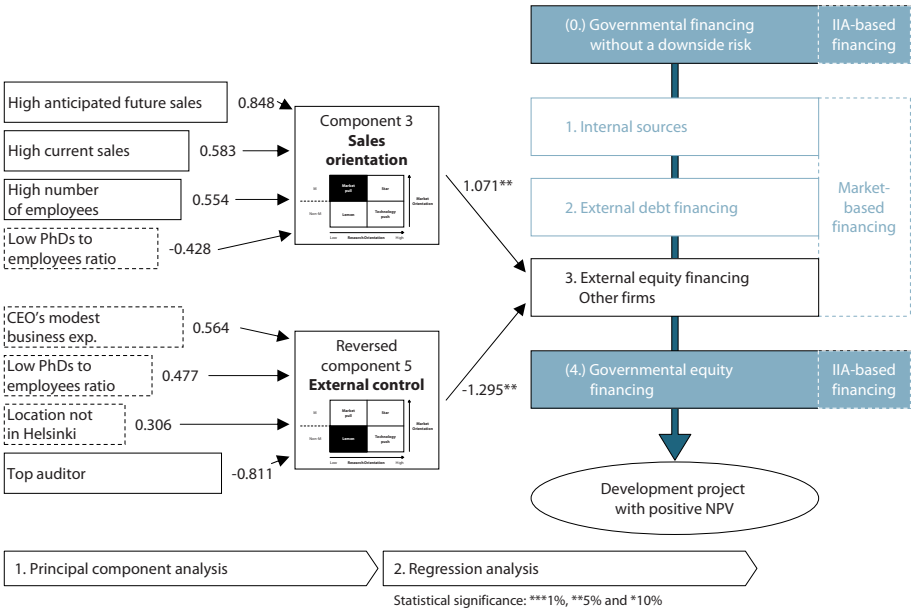
versity collaboration, company size, CEO experience, and equity financing from venture capital companies and other firms. High current sales seem to provide provide an important source of financial injections for R&D activity – as suggested by Kamien and Schwarz (1978) – although the Sales orientation strategy within the data seems to refer specifically to high anticipated future sales, rather than to high current sales.

Interestingly, the pattern of financial inputs of venture capital companies and high R&D intensity (component 6) is in line with the findings of Baysinger et al. (1991): they concluded that high ownership stakes of institutional investors imply high R&D intensity.

External equity financing: other firms

Figure 6.9 presents results for companies financed by other firms as shareholders. Capital injections from other companies reflect an intensive market orientation with high current and anticipated sales closely related to type **M** companies. The

Figure 6.9 The strategic orientations of companies receiving equity financing from other firms



companies have a relatively large but non-research oriented employees. As described earlier, component 5 indicates a Lemon with type **non-M** corporate strategies, as it lacks both research orientation and market orientation, at least in terms of internal human resources. However, this is the case only when we consider component 5 an isolated phenomenon.

Companies owned by other firms can function in a very specific part of the parent firms' value chain. Consequently, the IPR portfolio and marketing functions can be transferred to any other part of the group as corporate functions (see Hermans and Kulvik, 2004). A company owned by another firm should hence be considered within the context of the entire group rather than as a sovereign entity.

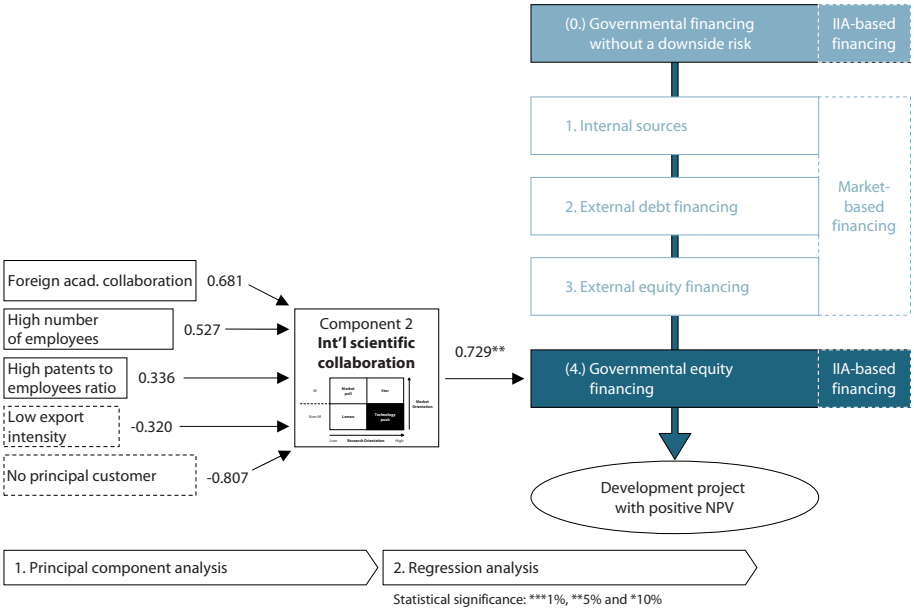
The difficulty that Finnish biotechnology companies faced raising money from initial public offerings at the beginning of this century links our findings to the work of Lerner et al. (2003). They suggest that during periods of limited external equity financing, US biotechnology companies were too compliant, shifting a large share of control to large outside partners. Reversal component 5 in our data is related to equity financing provided by other firms; it reflects a form of external control and monitoring similar to that found by Lerner et al. (2003).

Government equity financing

According to this study's hypothesis, companies are expected to turn to IIA-based government venture capital equity financing only as a last resort for positive NPV projects. Government venture capital organizations have financed companies showing a strong penchant for research but lacking a clear market orientation – type **non-M** companies (Figure 6.10). This is in clear contrast to the preferences of market-based venture capitalists (Figure 6.9). The empirical analysis shows, moreover, that the companies with market-oriented strategies have received all their financing from preceding market and non-market sources within the extended financial pecking order framework.

Lerner and Merges (1998) found that among US biotechnology alliances the partners with greater financial resources tended to have significantly more control rights within the relationship. In light of their finding, it is interesting to note that the companies that obtain significant government equity financing, as well as private venture capital financing, generally have control over a large patent portfolio. As Table 7.3 presents, government and private venture capital financing constitutes two thirds of the total equity financing. Therefore, it seems that IPRs are related to the firm's financial resources *per se*, rather than to the financing source.

Figure 6.10 The strategic orientations of companies receiving equity financing from government venture capital organisations



6.4.3 Sensitivity analyses

The study utilizes a relatively small set of cross-sectional data. This is associated with two potential problems:

1. Reverse causality between the dependent and independent variables.
2. Higher levels of sensitivity of results due to our limited number of observations.

First, the reverse causality issue suggests that it may be difficult to assess whether a company's strategic orientation is determined by its owners or whether the owners have been attracted by the company's existing strategic orientation, or some combination of these. Therefore, the validity of the implications based on the results above is directly related to the validity of the pecking order hypothesis. The pecking order theory assesses the financial decisions are made primarily by the companies, which aim to optimize the cost of financing. According to this reasoning, a company's strategic orientation should predict the sources of financing on which it will rely.

Second, the problem of increased sensitivity of results may be assessed by comparing the results produced here to those of alternative technical analyses. To that end, (1) a conventional principal component analysis without any rotation and (2) a generalized least squares (GLS) approach with the same rotation method as used above were employed. These alternative tests generated results aligned with those above, with a few exceptions (described below).

When the variable indicating whether the the company has received financing from Tekes on the unrotated principal component scores was regressed, four significant components were found, instead of only the two that emerged from the original analysis. This is due in part to the unrotated model's inability to simplify the components: the sensitivity analysis results in two components with high loadings on current and anticipated future sales. In addition, the first of these components had a high loading on the Helsinki region and another on the Turku region, whereas the rotated model was able to simplify the sales loadings within single components, with no loadings on a geographic location.

The clearest difference between the GLS model's results and the original ones was linked to the government venture capital institution. In this model, features associated with the research-oriented factor included collaboration with international academic institutions and the number of employees as above. The research-oriented factor also showed high loadings on anticipated future sales but not on any other measure of market-orientation. Thus, according to the GLS model companies financed by the government VC expect high earnings in the future from their internationally oriented research.

6.4.4 Discussion on empirical findings

Government institutions in Finland, as in many other countries, have placed strong emphasis on advancing the biotechnologies as a basis for drug development, although the pharmaceutical industry has not been historically one of the industrial pillars in Finland (Hermans and Kulvik, 2005). Finland's existing policies imply that the government has based its industrial and innovation policies on the conventional infant industry argument, with high hope pinned on business opportunities in the pharmaceutical markets.

The government institution (i.e. Tekes, in the data) provides direct subsidies. Tekes also provides loans without requiring collateral, and if the project fails, the loan becomes null and void. According to the extended financial pecking order, such a financier should become a primary source of financing for any kind of company. This was indeed confirmed by the fact that nearly all the companies in the sample

applied for government direct subsidies, though only 65% of the companies ultimately received them. Furthermore, principal component analysis suggested that 65% of the subsidized companies express both market and research orientations, and thus represent both types **M** and **non-M** companies.

The government takes on the business risk for the companies, and thus enables them to seek higher earnings by developing their products through later stages. The financial pecking order is not distorted, but it could have a detrimental effect on the company's commercialization strategy as it weakens the quest for early sales and thus the drive for commercialization. This notion was supported by this study's findings,[5] specifically where component 2, "*International scientific collaboration*", seemed to increase the probability of obtaining government subsidies, but to decrease the probability of generating any internal sources of financing when named as "*Foreign principal customer*". Accordingly, the (international) market orientation, rather than the (international) research orientation, seemed to boost the company's positive earnings and equity financing from entrepreneurs involved in the business activity.

The government institution willing to perform equity financing (i.e. Sitra, in the data) was expected to remain the last resort in the financial pecking order for any type **M** or type **non-M** company. The reasoning underlying this prediction was related to the additional risk of arbitrary decision-making on the part of the government VC due to the disconnection of power, responsibility and changing political climates, leading to a negative signaling effect. This could discourage the most promising type **M** companies from even applying for any government VC financing; and consequently the government VC equity financing would attract only **non-M** companies, which are often unable to obtain adequate financing from any other source. This seemed to be the case in the empirical analysis. Sitra was connected only with a research-oriented component, and thus with **non-M** companies.

The findings might also reflect an explicit strategy on the part of Sitra, such that the organization had decided to support promising high-risk companies that would otherwise not survive. As **non-M** research companies are inherently associated with high hopes and high risks, effective risk management requires the investor to be involved with a sufficient number of companies in order to offset the technical failure of a single project. Sitra is an early-stage investor; the typical success rate for a pharmaceutical product in preclinical testing is 0.4% (DiMasi et al., 2003). This would require 250 projects to yield one success, on average. Suc-

[5] This was confirmed also by the simpler measures: the Pearson correlation between the zero-phase government financing vs. internal financing was negative ($p<.05$).

cessful pursuit of such high-risk ventures requires a very solid investment capacity and an enduring strategy.

This study's theory-based assertions and empirical findings point to potentially inefficient use of tax-payer money: when the government VC provides equity financing directly to companies. In such a case, the attractiveness of investee companies may be damaged, as government VC equity financing may signal to other (private) investors that the company is incapable of convincing market-based financiers to invest, given that taxpayer money represents a significant stake in the company.

A potential remedy could be a network of financiers. If the government VC acted as a part of the financiers' community, then it might co-invest with private counterparts.[6] The second, potentially more sustainable cure could be to acknowledge these structural shortcomings and realign interests. A government VC could act as a fund of other external private funds and outsource direct ownership to private players, while it could still direct the financing selectively to those fields that fall under the infant industry argument.

In the industry's point of view, Kamien and Zang (2000) showed that a creation of a competitive research joint venture reduces the level of technological improvement and increases prices compared to when firms conduct R&D independently. Their findings direct further analysis to assess the significance of collaborative patterns between the companies more thoroughly.

6.5 Conclusions

The infant industry argument aims at generating new, economically significant industrial clusters that will provide a competitive edge for firms entering global markets. This study analyzed the impact of public financial instruments implemented in accord with the infant industry argument.

The hypothesis was that an infusion of government financing into infant-industry companies extends the financial pecking order and thus modifies company strategies for two primary reasons:

1. If free government subsidies are available or if repayment conditions of government debt financing are not as stringent as those of other loan providers, the government subsidies and loans could be the first-preferred financial

[6] In our data, this was often the case. The basis for such cooperation is probably the origins of Finnish private VCs active in the biotechnology business: there are two private VCs active in the field and both are spin-offs of the government VC, Sitra, which has a stake in the private VCs. Therefore, one can expect close collaboration between the institutions, at least on a temporary basis.

instruments even over companies' internal financing, and hence would occupy the first rank in the pecking order. As the government takes on risk for the companies, the companies can strive for higher earnings by developing their products into later stages.

2. If a government institution provides equity financing and aims at being a company shareholder, this could impact the opposite end of the pecking order. This is due to principal-agent problems, and the potential threat of political climate fluctuation directing the behavior of government institutions as shareholders with the negative signaling effects resulting from such changes of behaviour. This should discourage entrepreneurs from applying for equity provided by government sources. In such a scenario the entrepreneur would prefer private equity investors over the government, placing the government last in the financial pecking order.

In order to assess the extended financial pecking framework, the capital structures of small and medium-sized Finnish biopharmaceutical companies were analyzed and the empirical findings viewed. The Finnish biopharmaceutical sector was chosen because it represents a specific infant industry where public financial instruments have been implemented.

The findings indicated that government interventions do affect the financial pecking order and corporate strategy. The results confirmed the extension of the financial pecking order as a relevant tool reflecting IIA-based policies in two regards. First, government subsidies and loans without stringent repayment conditions become the most preferred financial instruments, even over companies' internal financing. Second, taking on the government venture capital organization as the owner seems to be the last resort and a relevant option only for companies with clearly non-market oriented research-based strategies.

Based on this study's findings, government equity financing seems biased towards supporting non-market strategic orientations of the companies. As an alternative, one could ask whether temporary tax reliefs could encourage the more market oriented private equity investments into the infant industry.

From a corporate perspective, the extended financial pecking order framework has some important applications and implications. Corporate managers may find the framework useful when comparing the distinct forms of private and public financing. Second, due to its transparency, the framework helps to create a dynamic plan for initial or further corporate finance. This, in turn, may adduct or even pair the corporate finance planning with IIA-based technology policy.

Appendix 6.1
Principal component analysis

KMO and Bartlett's test

Kaiser-Meyer-Olkin measure of sampling adequacy		0.408
Bartlett's test of sphericity	Approx. chi-square	160.342
	df	91.000
	Sig.	0.000

Communalities	Initial	Extraction
Lnperson	1	0.6819
post-graduated labor per total labor	1	0.4614
Lnceoexp	1	0.7641
rdcost/total cost	1	0.8511
patent applications + patents / labor	1	0.6224
Lnaget	1	0.6704
principal customer (>1/3)	1	0.8035
collaboration with foreign academic institutions	1	0.5831
Top5 auditor	1	0.7923
Lnto	1	0.7887
export/sales <=10%=0 >10%=1	1	0.7284
anticipated sales <8meur=0 >8meur=1	1	0.7773
Helsinki	1	0.8499
Turku	1	0.8465

Extraction method: principal component analysis.

Source: *ibid*.

Total variance explained

Component	Initial eigenvalues			Extraction sums of squared loadings			Rotation sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	2.730	19.497	19.497	2.730	19.497	19.497	2.035	14.538	14.538
2	2.164	15.458	34.955	2.164	15.458	34.955	1.948	13.917	28.455
3	1.700	12.144	47.099	1.700	12.144	47.099	1.759	12.565	41.020
4	1.371	9.790	56.889	1.371	9.790	56.889	1.701	12.150	53.170
5	1.245	8.894	65.783	1.245	8.894	65.783	1.491	10.651	63.821
6	1.011	7.224	73.007	1.011	7.224	73.007	1.286	9.187	73.007
7	0.926	6.613	79.621						
8	0.814	5.815	85.436						
9	0.691	4.934	90.370						
10	0.413	2.949	93.318						
11	0.341	2.439	95.758						
12	0.273	1.948	97.705						
13	0.202	1.446	99.152						
14	0.119	0.848	100.000						

Extraction method: principal component analysis.

Source: *ibid*.

Component matrix[a]

	Component					
	1	2	3	4	5	6
Anticipated sales <8meur=0 >8meur=1 (anticipated sales of the company in 2006 over 8 million euro, then 1, otherwise 0)	0.666	-0.166	-0.221	-0.153	-0.009	0.483
Lnto (sales, log)	0.540	0.406	0.212	-0.055	-0.375	0.379
Lnaget (age of the company, log)	0.539	0.399	0.375	0.126	0.138	-0.212
export/sales <=10%=0 >10%=1 (export per sales >10% then 1, otherwise 0)	0.463	0.437	0.451	-0.305	0.065	-0.150
Post-graduated labor per total labor (%)	-0.434	0.252	-0.129	0.387	0.205	-0.027
Principal customer (>1/3) (sales to a single customer exceeds 33% of the total sales)	-0.250	0.636	0.146	-0.344	0.300	0.326
Collaboration with foreign academic institutions (if yes then 1, otherwise 0)	0.370	-0.592	0.123	0.240	0.140	0.057
Lnperson (number of employees, log)	0.528	-0.575	-0.076	-0.090	0.157	0.184
Top 5 auditor (big int'l auditor 1, otherwise 0)	0.175	-0.531	0.374	-0.461	0.132	-0.331
Helsinki (location in Helsinki region 1, otherwise 0)	0.511	0.178	-0.659	0.199	-0.139	-0.255
Patent applications + patents/labor (number of patents and pat. appl per capita)	0.246	0.005	0.559	0.438	-0.016	-0.239
Turku (location in Turku region 1, otherwise 0)	-0.448	-0.314	0.482	0.313	0.204	0.419
Lnceoexp (Ceo's business experience in years, log)	0.506	0.229	-0.045	0.556	0.366	0.102
Rdcost/total cost (R&D expenditure to total cost ratio, %)	0.110	0.089	-0.288	-0.225	0.832	-0.075

Extraction method: principal component analysis.
All the indicators reflect the situation in 2001 if not other quote.
[a] 6 components extracted.

Source: *ibid*.

Rotated component matrix[a]

	Component					
	1	2	3	4	5	6
Lnaget (age of the company, log)	0.801	-0.025	0.068	-0.135	0.023	0.065
Export/sales <=10%=0 >10%=1 (export per sales >10% then 1, otherwise 0)	0.707	-0.320	0.167	-0.103	-0.294	0.045
Patent applications + patents/labor (number of patents and pat. appl per capita)	0.632	0.336	-0.180	0.189	0.037	-0.203
Principal customer (>1/3) (sales to a single customer exceeds 33% of the total sales)	0.115	-0.807	0.047	0.239	0.106	0.262
Collaboration with foreign academic institutions (if yes then 1, otherwise 0)	0.083	0.681	0.262	0.173	-0.087	0.082
Anticipated sales <8meur=0 >8meur=1 (anticipated sales of the company in 2006 over 8 million euro, then 1, otherwise 0)	0.008	0.156	0.848	-0.160	0.025	0.090
Lnto (sales, log)	0.443	-0.275	0.583	-0.111	0.114	-0.388
Lnperson (number of employees, log)	-0.042	0.527	0.554	0.001	-0.225	0.212
Turku (location in Turku region 1, otherwise 0)	-0.097	0.154	-0.097	0.882	0.151	-0.052
Helsinki (location in Helsinki region 1, otherwise 0)	0.039	0.204	0.150	-0.829	0.306	0.058
Top 5 auditor (big int'l auditor 1, otherwise 0)	0.106	0.291	0.013	0.125	-0.811	0.153
Lnceoexp (Ceo's business experience in years, log)	0.495	0.268	0.202	-0.083	0.564	0.284
Post-graduated labor per total labor (%)	-0.095	-0.111	-0.428	0.119	0.477	0.124
Rdcost/total cost (R&D expenditure to total cost ratio, %)	0.015	-0.085	0.034	-0.094	0.003	0.913

Extraction method: principal component analysis.
Rotation method: varimax with Kaiser normalization.
[a] Rotation converged in 16 iterations.

Source: *ibid*.

Component transformation matrix

Component	1	2	3	4	5	6
1	0.555	0.318	0.638	-0.417	-0.069	0.074
2	0.430	-0.760	-0.119	-0.257	0.397	-0.004
3	0.616	-0.034	-0.100	0.652	-0.343	-0.257
4	0.208	0.515	-0.258	0.118	0.760	-0.183
5	0.147	0.044	-0.072	0.272	0.091	0.943
6	-0.251	-0.228	0.705	0.497	0.367	-0.075

Extraction method: principal component analysis.
Rotation method: varimax with Kaiser normalization.

Source: *ibid*.

Appendix 6.2
Logistic regression results

Independent variables:	Component 1	Component 2	Component 3	Component 4	Component 5	Component 6	Constant
	Established business (+)	Int'l scientific collaboration (+)	Sales orientation (+)	Location in Turku (+)	Human resources (+)	Research and development (+)	
	Lemon (-)	Foreign customer (-)	Scientific experts (-)	Location in Helsinki (-)	External control (-)	Sales (-)	
Dependent variables:							
Infant industry argument-based financing							
(0.) Governmental financing without a downside risk	-0.097 (.683) **non-M**	**2.492**** (1.092) **M**	**4.055**** (1.601)	-0.909 (0.746)	-0.459 (0.568)	1.891 (1.174)	**3.302**** (1.266)
Market-based financing							
1. Internal sources: positive earnings	**1.846*** (1.024) **M**	**-2.998*** (1.759) **M**	0.370 (0.344)	-0.227 (0.511)	1.377 (0.908)	-3.203 (2.052)	**-2.303*** (1.255)
1. Internal sources: entrepreneurs' equity financing	-0.207 (0.452)	**-1.480***** (0.545) **M**	-0.712 (0.452)	-0.673 (0.487)	**1.081**** (0.506) **M & non-M**	0.235 (0.442)	-0.013 (0.428)
2. External debt financing: debt from banks	0.600 (0.492)	-0.021 (0.492)	0.273 (0.447)	-0.338 (0.509)	-0.607 (0.529)	-0.264 (0.454)	**-1.840***** (0.523)
3. External equity financing: venture capital companies	0.501 (0.504)	**1.682**** (0.674) **non-M**	**1.144*** (0.635) **M**	1.202 (0.733)	-0.559 (0.770)	**1.156**** (0.505)	**-2.278***** (0.838) **non-M**
3. External equity financing: other firms	0.540 (0.486)	-0.349 (0.496)	**1.071**** (0.479) **M**	-0.348 (0.494)	**-1.295**** (0.608) **non-M**	0.069 (0.412)	**-1.372**** (0.534)
Infant industry argument-based financing							
4. Governmental equity financing	-0.113 (0.343)	**0.729*** (0.378) **non-M**	0.064 (0.340)	0.219 (0.356)	0.007 (0.377)	0.453 (0.346)	-0.567 (0.357)

Statistical significance: *** 0.1%, ** 1%, * 10%.

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Section III

Recommendations for Optimal Industry Performance

CHAPTER 7

BRIDGING THE GAP IN TECHNOLOGY TRANSFER BETWEEN ACADEMIA AND INDUSTRY

A case study on the impact of Bayh-Dole on technology transfer at US universities

Antti-Jussi Tahvanainen – Raine Hermans

7.1 Introduction

7.1.1 Background – government intervention, academic research, and their impact on health care stakeholders

As has been explained in the previous chapters, government choices regarding the ultimate payer, IPR policies, regulation of drug development, price regulation, and technology development subsidies all affect the dynamics of health care systems, particularly the strategies and operational preconditions of the biotechnology industry.

In this chapter the prior analyses are expanded by examining the impact of the Bayh Dole Act of 1980 on the establishment and practices of university technology transfer offices (TTOs). That TTOs have become particularly important is evidenced by the fact that commercialized biotechnology inventions originate from academic research. The focus here is on the role that U.S. TTOs play in matching the substance of academic research with the need-driven demand of commercial markets.

The evaluation of the success of TTO activities will not only focus on the traditional measures of revenue streams, deal flows, or start-up frequencies, but also on other, less quantifiable, benefits. Capturing these impacts in future research will be a formidable but necessary challenge when comparing different technology transfer mechanisms.

7.1.2 The intervention meaning in English? – a brief account of the Bayh-Dole Act

As the focus of the chapter will be on the micro-level analysis of the role of TTOs rather than the impulse that caused them to be estanlished in the first place, the Bayh-Dole Act as the major government intervention widely responsible for the emergence of TTOs is dealt with only briefly here.

The Bayh-Dole Act, also called the University and Small Business Patent Procedures Act, regulates intellectual property that arises from research funded by the federal government. The act was enacted by the United States Congress in December, 1980, providing US universities, small businesses, and non-profit organizations with the right of ownership to the inventions and other intellectual property resulting from such funding. Prior to the enactment the title belonged to the federal government, the funding agency.

To retain the title, the recipient of federal funding has to fulfill a set of requirements:

1. The recipient must actively promote and facilitate the commercialization of the invention.
2. The recipient must protect the invention by filing for a patent or a suitable form of protection.
3. The recipient must compensate the inventor by sharing the royalties arising from the application of the invention.
4. The recipient must prefer the domestic (US) industry and small businesses when promoting the commercialization of the invention.
5. The recipient must claim title to the invention within a certain time.
6. The recipient must inform the funding agency of inventions disclosed by researchers.
7. The recipient must grant to the federal government a non-exclusive, irrevocable, non-transferable, paid-up license to practice or have practiced on its behalf throughout the world.
8. The recipient must utilize the residual proceedings from the commercialization of the invention for education and research.
9. The recipient must not assign the rights to the invention.

In the light of the focus, requirements one through five, in particular, are of interest, since they have given rise to the establishment of technology transfer offices in US universities. The tasks related to fulfilling the requirements necessitate in-depth expertise in a broad set of areas including intellectual property rights, patent legislation, the very substance of science and research, administration, and

the commercialization of technology including marketing and strategizing. They entail reaching out beyond the boundaries of the university and actively engaging in the development of the surrounding economy.

For the traditional administrative organs dealing with the university's conventional affairs, the many tasks and necessary related expertise proved too extensive to handle with conventional resources. There was a need for a designated unit that could tackle the obligations imposed by the Bayh-Dole Act and could support the university in its extended mandate that now included the commercialization of research. Hence, the TTO was born.

7.1.3 Limitations – a word on the generalizability of implications

Before proceeding with the actual analysis a few facts relating to the setting in which this study was carried out must be pointed out. First, the results of this study are not general. They are not intended to represent most US TTOs nor a model of the average university technology transfer office. The aim of the study is not to provide a general description. Rather, using a handful of the most successful cases by more traditional and quantitative measures, the intention is to approximate *the ideal* of a TTO's role in technology transfer as constructed from the underlying cases. This comes inevitably at the cost of statistical significance, since it is more about sense-making than making generalizations.

Second, TTOs operate in strongly local environments. Some offices in this sample are embedded in unique environments especially conducive to the transfer of technology. Thus, implications drawn from the results must be understood in their specific environmental contexts and interpreted with care in others. Attention has been paid to include necessary environmental aspects in the analysis to facilitate such interpretation.

Finally, it is recognized that technology transfer is a complex process in which TTOs play just one of many roles. A TTO is not an isolated instance capable of providing value to the process detached from its systemic environment comprising regional entrepreneurial culture, governmental funding of research, the availability of risk financing, etc. Thus, it is paramount to recognize that the present study is an in-depth analysis of one of the central parts of the process and not of the entire process. It follows that the value created by TTOs cannot be defined by measuring the overall success of technology transfer, since it is not solely attributable to the activities of TTOs. Instead, the focus must be on identifying the *added value* that TTOs provide to the process.

The chapter is structured as follows. The next section presents a brief treatment of the positioning of the analysis within the existing relevant literature followed by a section dealing with the underlying data and methods of the study. In the subsequent section, a generic blueprint of the typical transfer process will be provided in order to give an initial overview of the tasks performed by the TTO. Then, reverting to Edvinsson and Malone's (1997) Value Platform Model, the theoretical framework of the study, which will serve as a structural guide and point of reference against which the data and arguments are reflected, is constructed. The subsequent section constitutes the analytical core of the study and incorporates the results of applying the Value Platform Model to the underlying data. The final section concludes the study by presenting the most central implications to managing the process of technology transfer between academia and industry.

7.2 Previous research and data

7.2.1 Literature – an overview of the body of knowledge on TTO activities

As is the case with most of interdisciplinary studies, there is plethora of existing literature from sometimes very distant fields of research among which the particular study must be positioned. In this case the relevant literature is found in the areas of knowledge management and intellectual capital (IC), on the one hand, and in the area of technology transfer, specifically technology transfer organizations, on the other. While the IC literature is mainly theoretical in nature, the organizational research-oriented literature in technology transfer provides a much broader set of empirical studies. Since the relevant IC literature will be discussed in detail in building the theoretical background for the analysis, this overview will be limited to technology transfer studies. While the IC literature suits the theoretical aims it is the technology transfer literature that is of interest thematically.

Among many single studies, Chapple et al. (2005) analyze UK university TTOs on their performance based on the volume of annual license agreements, invention disclosures, and total research income. They find that new licensing is positively correlated with the research intensity of regions and the presence of medical schools at the universities. These results will be corroborated later on. Furthermore, Chapple et al. (2005) argue that the size of the TTO, as well as the total research income of the university, affect the performance of the office, a finding also supported by the data in this analysis.

Siegel et al. (2003) assess the relative productivity of US TTOs. In line with the results of this chapter, they find that the performance is affected by environmental and institutional factors. Based on a qualitative approach Siegel, Waldman and Link (2003) further find that cultural barriers between universities and industry, as well as compensation, staffing, and reward practices, also explain TTO performance to respective extents. While their findings on the cultural, environmental, and institutional factors are supported also by the results of this analysis, the efficiency of reward and compensation schemes will be criticized below, as well as those performance indices based on monetary outcomes or the sheer number of licenses or protected IPR, for example.

Observing 11 case studies of inventions made in universities, Colyvas et al. (2002) investigate the roles that patenting and TTOs play in transferring university inventions onto markets. They find that the transfer of embryonic inventions, in particular, benefit greatly from intellectual property protection by the TTO, while in other cases transfer would have occurred anyway. Colyvas et al. (2002) also provide evidence of the central significance of TTOs' marketing efforts in cases where links between the academia and industry are weak. The latter finding will be extended by showing how marketing efforts are used to establish a bi-directional feedback loop that conveys information from the markets back to the inventor and vice versa.

Markman et al. (2005a) analyze which TTO structures and licensing strategies are most favorable for new venture formation, and which are correlated with each other. Distinguishing between for-profit TTO structures and non-for-profit structures, they find that for-profit structures are positively correlated with the formation of new ventures while non-for-profit structures relate positively to university business incubators. Similarly licensing-for-equity strategies correlate positively with new venture formation, while sponsored research licensing shows a negative correlation. A licensing-for-cash strategy reveals the least correlation with new venture formation. These results are somewhat at odds with the present observations because, among the most successful TTOs, no significant differences in structures or strategies as expressed in their mission statements and the ways they create value could be found. This is possibly due to the rather small sample and the focus on top performing TTOs.

Markman et al. (2005b) study commercialization speeds at US universities. They find that the generation of revenue streams and spin-off ventures is positively correlated to the speed with which TTOs are able to commercialize patent-protected technologies. Central determinants of commercialization speed, in turn, include TTO resources and competency as well as the active participation of the original inventors in the process. Complementing and supporting the findings of Markman et al. (2005b), rationales for the above mentioned relations are provided here. The

themes of competency, resources, and the participation of inventors are explicitly touched on here by empirically defining the essence of these aspects that is relevant to a TTOs success.

Parallel to Markman et al. (2005b), Lockett and Wright (2005) analyze the impact of university resources and capabilities on the formation of spin-out ventures. They find a positive correlation between the number of spin-out companies created and expenditure on IPR protection, business development capabilities of the particular TTOs, and the royalty regime of the university. While IPR protection as such is dealt with here only lightly, the analysis will provide rationales for the importance of business-related skills in TTOs.

Jensen et al. (2003) observe the TTOs practices in balancing the tensions arising due to clashing objectives of universities and their corresponding faculty. They find that TTOs adhere to the agendas of both parties and, as an agent, try to serve them as principals. As a central result, Jensen et al. (2003) show that a faculty's propensity to disclose an invention is dependent on its quality, the equilibrium licensing income, whether projects are sponsored research, and the inventor's rate of time preference. The analysis provides supporting evidence by showing that TTOs indeed operate under overlapping mandates of different stakeholders and providing some evidence of how such mandates can be aligned. Furthermore, it is argued that a faculty's propensity to disclose an invention is greatly affected mainly by two determinants: (i) the inventor's own preferences and motivation towards commercialization and (ii) the reputation of the TTO for being competent and able to show tangible results in advancing the given inventions along the technology transfer continuum.

There is a plethora of research that is similarly relevant from the perspective of this analysis (see, e.g., O'Shea et al., 2005; Lockett et al., 2005; Clarysse et al., 2005; Degroof and Roberts, 2003; Lockett et al., 2003; Di Gregorio and Shane, 2003) that cannot be fitted within the limited scope of the study. There are at least two excellent review studies that summarize the essence of scientific research on TTO activities. Von Ledebur (2008) reviews studies that pinpoint the differences in the institutional framework between Europe and USA regarding academic patenting and the organizational design of TTOs, while Rothaermel, Agung and Jiang (2007) go through over 170 studies related to university entrepreneurship in broader terms. One of their reviewed fields focuses on the productivity of TTOs.

While the above-cited literature relates to this analysis and supports the findings thereof in many ways, the present study still distinguishes itself in one central aspect from the existing literature: It is not the focus of this study to evaluate the performance of TTOs and the drivers thereof as such. Rather, the intention is to show *what* relevant performance is in the first place and *how* it is generated. Under-

standing what TTOs do helps to shed light on how performance should be defined, and gives an idea of whether and how such performance can, if even possible, be measured. Only then is it sensible to draw conclusions about the effectiveness of the TTO as an institution and evaluate the government intervention underlying its emergence.

7.2.2 Data – interviewing seven elite technology transfer offices

The data utilized in the present study are taken from three separate sources between April and October 2007. The central body of data was acquired by interviewing directors and, when the director was unavailable, high ranking technology transfer officers at seven prominent university technology transfer offices in the United States of America. All of the TTOs included met the criteria of being among the top 20 US university TTOs when measured by the number of start-ups founded in 2005. The number of start-ups was chosen, from among many other alternative measures of technology transfer activity[1], to identify highly successful offices, because it not only mirrors activity in the TTOs but also reflects the entrepreneurial environment in which the offices are embedded. As already touched on earlier, successful TTOs do not exist in a vacuum and this aspect is incorporated in our analyses. The interviews were conducted employing a semi-structured interview questionnaire that allowed the interviewees the freedom to answer in their own local contexts that differed from office to office in several dimensions (private vs. public university, self-sustaining vs. university financed, small vs. large office, multi-campus vs. single campus system, etc.). At the same time it ensured that all vital aspects of the Value Platform framework were sufficiently touched upon.

The second source of data was a large quantity of official and publicly distributed electronic and printed material concerning the activities of the TTOs interviewed. This secondary data, on the one hand, complemented the views provided by one person in each office and, on the other, verified their views against the official ones.

The third and final source of data consists of the comprehensive AUTM's STATT (Statistics Access for Tech Transfer) database that provided time series data on 21 important variables concerning tech transfer activities in around 160 US TTOs from

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[1] In addition to a rather high number of start-ups all but one office participating in the interviews have estimated to report close to 30 million $US for the current fiscal year in royalty income, which places them in the top echelon of US TTOs in royalties. Due to reasons explained in the analytical part of the paper, we did not utilize royalty income streams as a primary selection factor for participants.

1996 through 2005. The number of reported offices differed from one fiscal year to the other. The quantitative description of the US university tech transfer industry is based entirely on the STATT data.

The analysis uses direct quotes of interviewees who, for the purposes of obtaining unrestricted and in-depth comments, were promised complete anonymity. Therefore no references are given for the quotes.

7.2.3 Transfer process blueprint – the flow of TTO functions in a nutshell

The process from an invention's inception to the licensee is now given in Figure 7.1 to demonstrate where a TTO is positioned in the transfer of knowledge.

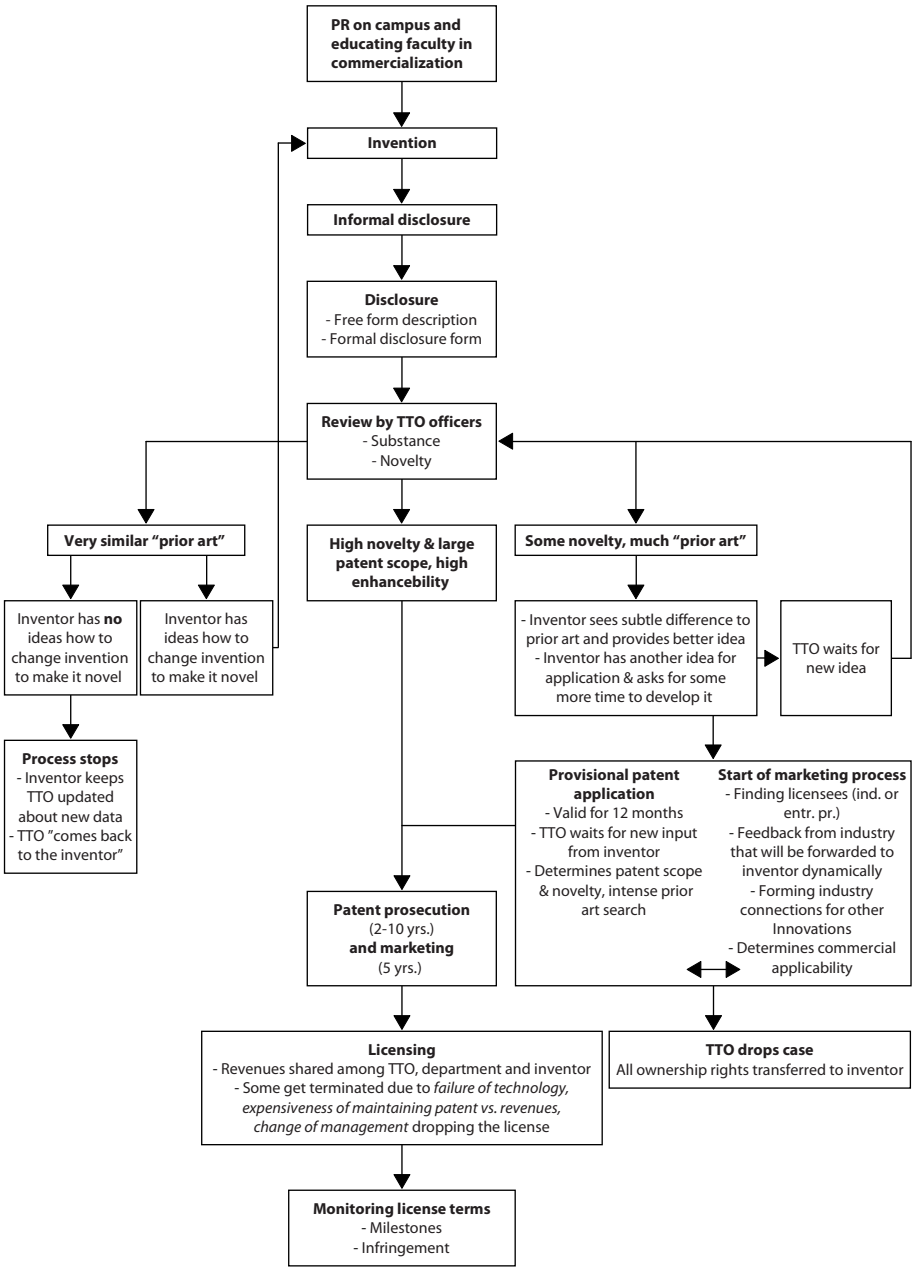
The process of technology transfer from the perspective of the TTO begins before an invention. The office often informs researchers and faculty aboutcommercialization through educational events, personal laboratory visits, expert guest speakers, weekly meetings, etc. encouraging inventors to disclose their achievements and submit an invention disclosure to the TTO. This might be informal at first and it is pre-reviewed by technology transfer officers. Should it seem promising, a formal disclosure is submitted to the office. This is usually a concise description of the invention and a standardized form.

The disclosure initiates a rigorous technical and prior art evaluation process at the TTO. With possible help from external patent offices, technology transfer officers search existing IPRs for potential hurdles in an attempt to determine whether the disclosed invention can be protected through IP protection. At the same time they also evaluate the technical feasibility and the potential impact of the invention with the prior art search being most important at this stage, however. Further action depends on the outcome of the prior art search. There are roughly three different outcomes.

First, there might be considerable existing prior art in the invention's field. In such an event the inventor is given the opportunity to change major aspects of the invention in an attempt add some novelty. The modified invention then starts over with a completely new disclosure. Should the inventor have no idea how to modify the invention the invention, it is not pursued further. The inventor is free to come back once novel ideas emerge, and usually keeps the office up-to-date about the latest data and developments.

Second, in the event of moderate existing prior art and, hence, some novelty inherent in the invention, the inventor is asked to show how the invention can be sufficiently distinguished from existing technology. The inventor can provide proof

Figure 7.1 Transfer process blueprint



in the form of more detailed data, for example, but might also have ideas how to apply the invention in a different way than previously intended. The TTO waits until the invention is modified, if necessary, and begins the next phase, which is filing a provisional patent that is valid for 12 months. During that period the inventor can make further modifications and improve the invention. Simultaneously, the TTO determines the novelty of the technology by an intense prior art search and decides on the final scope of the final patent. Moreover, the TTO begins to market it extensively by (i) finding a potential licensee for the up-coming IPR around the invention; (ii) gathering feedback on the commercial potential and applicability of the invention directly from the relevant industry. The feedback is forwarded to the inventor who is then able to make the appropriate modifications in an attempt to adapt the invention to industry requirements; and (iii) expanding the TTO network of industry connections that can be tapped into when marketing future inventions. Often, the inventor is said to be the best source for potential applicants of the invention.

Depending on the outcome of the final prior art search and the industry feedback, the invention is either dropped (the rights to the invention are often then transferred to the inventor) or the proper patent is applied for. This can take anywhere between two and ten years after which the invention is protected. Simultaneously, the marketing efforts continue for several years or until the invention is licensed. Once licensing occurs, the ensuing royalties are shared between the inventor, the university department, and the TTO. An active license is monitored by the TTO for agreed milestones (e.g. the invention has to be commercialized within a frame of X years from the date of licensing) and possible patent/license infringements. In time, some licenses might also be terminated by the licensee because, for example, the technology fails in the marketplace, the patent maintenance is too expensive relative to generated revenues or for strategic reasons.

Third, the initial prior art and technical evaluations might indicate that the invention is highly novel, offers a wide scope for patenting, and is highly upgradable through follow-up inventions. These are the most sought after inventions. In such an event, the TTO initiates full-scale patent application, marketing. and licensing efforts and bypasses the provisional patent.

Before reviewing the theory behind the analysis, it should be pointed out that the above description of the transfer is very general. It does not capture the subtler or more noteworthy differences in practices across the over 190 TTOs currently active in the US. Nor does it go into the details of micro-level tasks of the office. These will be analyzed after the theory.

7.3 Value platform – a theoretical framework providing structure

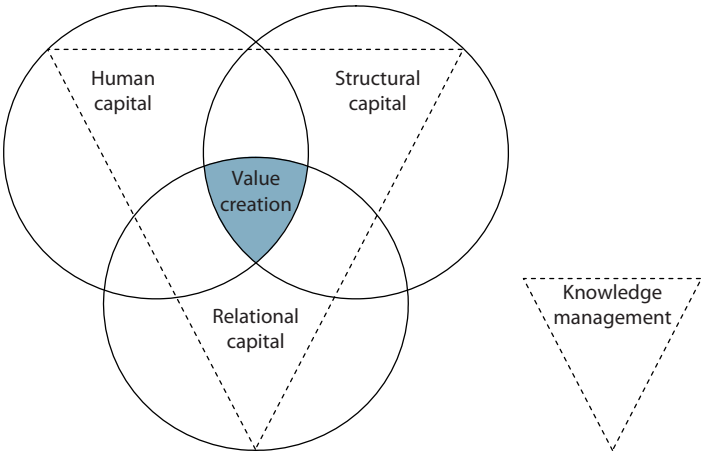
This section provides the theory behind the analysis Specifically, the Value Platform framework as first presented by Saint-Onge et al. in Edvinsson and Malone (1997) will be used. Additionally to being the central theory, it will also determine the flow of the analysis due to its rather concise nature.

To rationalize the application of the Intellectual Capital (IC) and Knowledge Management (KM) based approach on understanding the determinants of success and value creation in technology transfer one has to think about its substance and about what technology is in the first place. As will become apparent in the interviews later on, university technology is only very rarely tangible before it is licensed for further development. During the transfer from the university science lab to industry, technology is transformed from an initially very intangible state of knowledge, existing only in the mind of the inventor, to a slightly more tangible or codified form of knowledge as written down in a patent or other physical epitome of intellectual property.

Thus, the task of a TTO is to understand, protect, and sell, or in other words to transfer, *knowledge* created by one party to another. This, in turn, necessitates a vast array of specific knowledge, relationships, and support structures, as will be shown in detail in the analyses in the next section. What is most important to note is that there are very few, if any, tangible assets to be managed. If the contracts and the computer hardware that databases are maintained on are not deemed central to the process, then the university technology transfer leaves no physical trail to be traced. The whole process is about managing knowledge, or intellectual capital, as shall be argued later, inherent in external parties and the TTO itself. Thus, the utilization of the IC framework is a well-argued approach for analyzing the prerequisites of success in university originated technology transfer.

Edvinsson and Malone (1997) discuss the significance of IC to an organization. The essence of the discussion is the ability to give a holistic view on organisational development. Usually, IC is defined as consisting of three components, human, structural, and relational capital. IC provides a framework enabling all of these dimensions to be viewed in relation to each other. Even when two dimensions are very strong, the weak or inadequately managed third dimension of the value platform model presented in Figure 7.2 disrupts the value creation process. According to the model, it is the intersection, or more tangibly, the dynamic interaction of all three components that forms the basis for value creation (Saint-Onge et al. in Edvinsson and Malone 1997). In this chapter the prime objective is to show what

Figure 7.2 The value platform model



Source: Saint-Onge et al. in Edvinsson and Malone (2007).

value is in the context of TTOs. Knowledge management can be seen as a force pulling distinctive components into closer interaction with each other thereby maximizing value.

The merit of the IC platform is that three central dimensions of organisational development activities are considered in a single comprehensive framework emphasizing the importance of their balanced interaction (Mouritsen et al., 2000).

There follows a brief description of each of the three components forming the concept of IC. The actual analysis is discussed in the subsequent section. For further discussions, see MERITUM project (2002), Bontis (2002) and references therein.

7.3.1 Human capital

Human capital is defined as an individual's *knowledge, experience, capabilities, skills, creativity,* and *innovativeness* (Edvinsson and Malone, 1997). These are interconnected and collectively contribute to success in work (Ranki 1999). Sveiby (1997) uses the concept "*employee competence*", which he defines as the capacity to act in different situations to create both tangible and intangible assets.

The *ability to perceive changes* in the operational environment is also included in human capital (Edvinsson and Malone, 1997). This encompasses also learning. Learning is the development of an individual. It is an *adaptation to a changing envi-*

ronment or a potency to change the environment. These changes require the ability to control immediate work tasks, as well as the ability to improve operations and a readiness to develop even qualitative features of work (Salmenperä et al., 2000). *Attitudes* are related to this readiness, because they show what kind of a stance a person takes towards the tasks (Mayo and Lank, 1994).

The fact that an organization cannot own its human capital distinguishes this component of IC from other company resources (Edvinsson and Malone, 1997). Uncertainty about an employee's commitment to the organization reduces the organization's willingness to make these investments, especially if the required skills are non-specific and transferable (Albert and Bradley, 1997). Yet, competent personnel are the key to a company's endeavor to realize and develop its business ideas (Hansson, 2001; Sveiby, 1997). Investments in personnel are as crucial for knowledge-intensive organizations as a mass producer's investment in tangible assets (Sveiby and Lloyd, 1987).

7.3.2 Structural capital

Structural capital includes *patents, concepts, models, computer and administrative systems,* and *organisational culture* (Sveiby, 1997). Edvinsson and Malone (1997) define structural capital as the *context, empowerment of employees, structures supporting human capital, organizational capital, innovation capital,* and *process capital*. Empowerment of the employees is based on distributed decision-making and collaborative leadership models, aimed at inducing employees to commit to the organization and its goals. Structures that support human capital include, for example, recruiting capabilities, organizational culture, development activities, and motivating strategies. Organizational capital consists of systems and tools, enhancement of knowledge flows, and organizational competence. Innovation capital includes an organization's renewal capability, results from innovativeness protected by intellectual property rights, as well as results that can be used to create new products and services and develop them quickly into applications. Process capital is practical knowledge including definitions and improvements of work and production processes (Edvinsson and Malone, 1997).

An organization's knowledge base accumulates from numerous daily decisions and experiences. These are stored in *work processes, instructions, forms* etc. resulting in organizational learning. Organizational culture can be seen as a consequence of organizational learning as it forms a shared framework for defining and solving problems. Schein (1992) associates organizational culture with leadership and defines them as different sides of the same coin.

According to Edvinsson and Malone (1997) structural capital includes all the *codified knowledge and organizational structures* a company has created utilizing its human capital, or otherwise acquired for the organization. Organizational structure, different documents, databases, and all intellectual property rights (patents, trademarks, copyrights etc.) are included in structural capital. Unlike human capital, the company owns its structural capital and, therefore, it is also able to sell specific parts of it, such as the databases.

7.3.3 Relational capital

The relational capital includes all *external relationships with customers, suppliers,* and the *organization's collaboration networks* (Edvinsson and Malone, 1997; Sveiby, 1997; Stewart, 1998). In the context of a TTO this translates into potential licensee's (industry and start-ups), faculty inventors, and collaboration with other parties important to the process of technology transfer. In the traditional knowledge management literature concepts such as *customer capital, networking,* and *virtual organisations* have been associated with relational capital.

Customer capital consists of the strength and loyalty of the customer relationship. In this context the customer would be the industry searching for a license or the entrepreneur willing to license university technology to build a commercial enterprise around it. Such characteristics as *satisfaction, durability, price-sensitiveness,* and *good financial performance* of long-term customers are related to this category (Edvinsson and Malone, 1997). Customer capital can be created by committing the customers to the organization's activities using time and resources. An enduring and trustful relationship between the organization and the customer is the key element. Relationships are judged based on penetration, coverage, and loyalty measured as a customer's probability of continuing the partnership (Stewart, 1998). Even in the context of technology transfer offices maintaining long-term relationships with existing licensees is valuable in a number of ways.

Even though networking is seen as beneficial to a company, it has multifaceted effects on it. Breaking a commitment to some relationships and building new ones can result in significant costs. The reluctance to accept these costs reduces an organization's mobility in its relationships and may hinder its innovativeness (Håkansson and Ford, 2002).

Due to the increasing need for networking, organizational boundaries lose significance. Collaboration leads to co-operative systems, such as virtual organizations lasting for a while. Information technology can be used to improve the functioning of the value chain both inside organizations and between them (Salmenperä et al., 2000).

7.4 The value creation logic and added value of successful TTOs – impact, not income

The value creation logic of successful US TTOs is illustrated by showing how the interaction of the IC components described above is managed to add value to university technology transfer. In doing so, as defined at the beginning of this chapter, the aim is to demarcate the role that US university technology transfer offices (TTOs) play in matching the substance of academic research and the need-driven demand of commercial markets. This, in turn, gives rise to implications of the (indirect) effects that the Bayh-Dole Act left in its wake.

As touched on earlier, success in technology transfer from the university laboratory to its ultimate application on markets of any kind cannot be solely attributed to the activities of TTOs. There are many factors external to the TTO that contribute to the diffusion of technology in society. Local, regional, and international infrastructure, IPR legislature, technology policy agendas and programs, national innovation systems, entrepreneurial culture, availability of risk financing, and the role and mission of universities in society are all major factors affecting technology transfer. To make things even more complex, they might differ significantly from region to region affecting the outcome of the transfer even if the respective TTOs are identical copies. Thus, the value created by technology transfer cannot be attributed solely to TTOs, nor can it be argued that the value created by TTOs is identical across all regions.

In the light of the above claims and the research agenda, the perspective on those aspects of value that are attributable to TTO activities must be narrowed. Thus, the question is what is the *value added* provided by the offices. What are those unique services that the TTO contributes to technology transfer as a whole and, thereby, furthers its progress? A structured way to approach the matter is to determine first the general mission of TTOs and then to dissect the mission into more tangible value adding services.

7.4.1 General mission

In terms of the general mission the participating TTOs provided a rather unanimous definition. According to their views, a university TTO's mission is *to facilitate the transfer of university technology to the public sector and commercial entities, be they existing industry or newly formed start-ups, to be developed into products for the benefit of society while preserving the university's primary mission of education and research*.

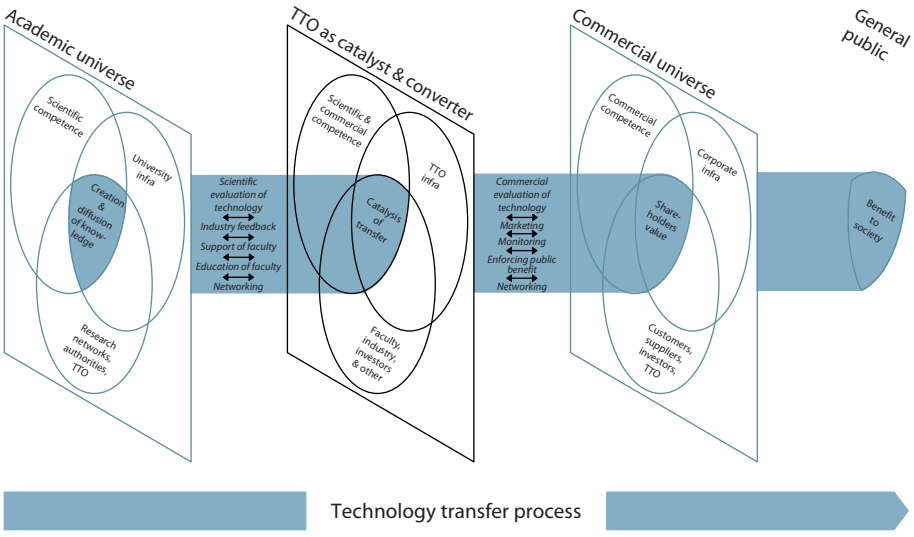
While being very comprehensive in nature, the general mission statement lacks the particulars necessary to make inferences about the concrete nature of a TTO's value creating activities. What it provides, however, is pointers at those domains that need to be scrutinized more in-depth to arrive at sufficiently detailed conclusions about a TTO's added value. Concepts like "*to facilitate*", "*for the benefit of society*" and "*preserving the university's primary mission*" all represent larger contexts that need to be analyzed further for sources of added value.

7.4.2 TTO as catalyst and converter

Figure 7.3 depicts the TTO's role in the transfer process by utilizing the value platform of the IC framework.

The data reveals that the TTO performs many functions that all aim at catalyzing the process by which knowledge created in universities is converted into technological applications. In doing so, the TTO operates between two worlds, the academic and the commercial, that are endowed with very distinct configurations of IC. From the perspective of knowledge management, it is these fundamental differences in the configurations that in part open up the infamous gap between

Figure 7.3 The TTO as catalyst and converter in the tech transfer process



the academic and commercial worlds stalling the transfer of technology. Figure 7.3 shows the rather generic value platform blueprints of the TTO, as well as both the academic and the commercial worlds. The light gray beam breaching through each platform signifies the value creation process of the system as a whole, which is driven by the tangible, catalytic functions performed by the TTO in cooperation with academic and commercial entities. The progress is not to be interpreted as unidirectional or linear. On the contrary, it is a bi-directional link that allows for feedback loops between the academic and commercial worlds as facilitated by the TTO. The process will be scrutinized in more detail in the following. But first why is a catalyst such as the TTO needed?

7.4.3 The gap between the academic and commercial worlds

Comparing the value propositions each of the two worlds aims to implement crystallizes the essence of the challenge in bridging the gap. While the academic world strives for the creation and free diffusion of pure knowledge as the ultimate goal, a commercial entity's priority, be it existing industry or an entrepreneurial start-up, is to provide the highest possible shareholder value to its stakeholders. This is usually achieved by exclusive ownership and strong restrictions on the diffusion of proprietary knowledge. The incentive structures of academics, on the other hand, are set up in a way that promotes the fastest possible publication of breakthrough research in order to further one's career and reap the ultimate academic merit. Simultaneously, this spells doom for commercialization attempts of research, because in competitive markets only technology that provides companies with an exclusive edge over others provides the incentives to invest in research and development that will take the emerging technology to the final markets.

Therein lays another challenge. The output of academic research is knowledge. Such knowledge is scientific in nature and constitutes merely very early stage technology, as it tends to lack the intention towards a market-driven and need-based application. Even at the licensing stage, university based innovations often are still starkly premature. Jensen et al. (2003) found in an empirical study of 62 US research universities that 50% of inventions licensed by their sample universities were only proof of concepts and another fourth were mere lab-scale prototypes. In contrast to academics, commercial entities live by meeting market needs through providing applicable technology. Thus, in order to arouse their interest in licensing a given discovery, companies need to be shown in an understandable and credible manner that the discovery can viably be developed further and reach sufficient market potential to offset the technological risk and investments inherent in such development.

Showing the potential, in turn, necessitates an in-depth simultaneous understanding of applied science and markets, a clear vision of how the former can serve the latter. Moreover, it requires the capability of communicating this vision across the boundaries of the academic and commercial worlds that are both characterized by strongly differing cultures, languages and mind-sets. From an IC perspective this calls for considerable overlap in at least the *human capital* and *relational capital* dimensions on both sides, which, generalizing to some degree, is rarely given. Slightly caricaturizing an everyday manifestation of the dilemma, the up to 60 slide long technical presentation of the enthusiastic scientist simply does not match the purpose of the typical elevator pitch highlighting success probabilities, return on investment rates, and market shares that investors and licensees are able to digest and require for decision making.

In terms of *relational capital* both worlds tend to have fairly detached networks that provide very distinct functions. While the relational capital of academic scientists comprises research networks among fellow scientists and contacts to authorities that affect the freedom to operate in laboratories through legislation, permits, and monitoring, the commercial entity represents a nexus of contacts with customers, suppliers, and investors. Except for industrial sponsored research that is the manifestation of a long-term relationship between industry and a given university laboratory, the commercial and academic worlds rarely share common relational capital that could serve as a natural channel to exchange knowledge inherent in human capital, the essence of technology.

With this all being said, the value created by the TTO consists of its many functions that either dissipate the gap between the academic and commercial worlds or bridge it. In essence, the core of the value created by the TTO is in the conversion of the value created by entities in the academic world in the form of knowledge into relevant input fed into the value creation process of the commercial world. The ultimate value to commercial entities and, thereby, to society does not accrue before that input is converted into applicable products or services. Below, each of the value adding functions of the TTO that comprise the mechanisms by which the technology transfer process is catalyzed and value is converted are briefly described in order to establish an understanding of a TTO's implemented added value. The detailed analysis of the dynamic interaction of single components of IC is left for further research ambitions. In its capacity as a catalyst and converter, the TTO employs the functions to first decrease the barrier to initiate the transfer of technology on both sides of the value creation continuum depicted in Figure 7.3, and then, in subsequent stages, to sustain the process until the technology in question is diffused in one form or another in society.

7.4.4 Value adding functions in the interface of the academic world

The academic world, epitomized by the individual inventor(s) in each particular case, is initially served with catalyzing functions in the form of educational services. These have the objective of familiarizing researchers with the concepts of protecting intellectual property and its fundamental centrality in commercializing results of research, providing guiding information about the supporting services provided by the TTO itself, offering detailed instructions and guidelines on what concrete steps to take if there is interest in commercialization, giving first insights into financing entrepreneurial activities and the role of investors in start-up companies, and so forth.

> "[We] educate students and faculty on everything from IP to how you go from just thinking about research questions to how products... how to go from the laboratory to the market."
> *– Director of the TTO of a private university –*

> "We will also host events. Anybody can show up, we will have an attorney who talks about patents, we will serve you pizza and send you students, and we will do such outreach events. We will do a start-up boot camp every couple of years. We all have panels of VCs and attorneys talk about this, again open to the public, anybody can attend, even people outside [the university] can attend, and we hope our faculty are motivated to come to these things. We can lead the horse to water, but it is up to them how they want to use their time as a [...] researcher."
> *– Assistant Director of the TTO at a public university –*

> "[...] you have to get word out to faculty. Our policy is to say that they are not obligated to disclose to us. If they want to commercialize, then it has to go through us. But if they want to publish it and not look at commercialization routes for their invention they are perfectly able to do it. It is not a simple matter. But you have to get out there to faculty and try to get to department meetings [...], so they will listen to you.
> Technology licensing is not often high on their list. The younger people are interested in getting tenure and that involves publications and does not involve licensing. And you also have to make sure that they have confidence in you. Otherwise, if they think you are incompetent, they are not going to give you their technologies, because they are going to think it is a waste of time.
> [...] The faculty are like anything else. They are a Gausian distribution. There are those that are very highly interested in the commercial application of their technology, they want to see it out there; they want to get their financial share. We have made several millionaires from faculty. And then there is the other end that are pure academics. They want to do their research and publish and could not care less. I don't think you are going to ever make much of an impact on those that do not really care about it. I think [to] the ones that are highly motivated and are commercially motivated you have to show to them that you are capable of getting the technology [licensed].
> [...] I think getting them to disclose is not the issue; showing them that you are savvy and able to license the technology [is]. There is the other zone that you have to get out there and educate them to some degree and try to get them thinking about what you are doing."
> *– Director of the TTO of a public university –*

The aim is to activate researchers and inventors to become interested in the commercial opportunities and encourage them disclose their results to the office by lowering inhibitions attributable to the lack of interest in, knowledge of and familiarity with these issues. To this end the TTO utilizes its own interdisciplinary human capital (HC) comprising scientific as well as business knowledge and its relational capital (RC) in the form of expertise from law firms, different financial institutions, and entrepreneurs. The knowledge inherent in HC and RC is channeled through the TTO's structural capital (SC) to the faculty. SC relevant to educational functions finds expression in established educational events on campus, regular laboratory rounds and related liaison activity, and business courses arranged jointly with local business schools.

> "In terms of the faculty members we did something: They had a course run by the [local] business school [...]. We had an all-day course for faculty members, and they would just go over the whole thing, you know, about patents, mostly about entrepreneurship, about starting companies. We particularly invited those young, very bright, but sort of naïve and who are not really thinking about these things and are more concerned about papers and stuff like that. [...] it was a great success. That's probably going to be an on-going thing. [...] In physical sciences we meet once a week, [...] we sit down and talk about new inventions that have come in. It is mainly marketing oriented. [...] so they are very active in meeting with faculty members."
> *– Director of business development at the TTO of a private university –*

Generated value of educational functions is evident in a given faculty's increased propensity to commercialize its research and could be measured by the number of disclosures per dollar of federal research funding, for example.

One of the most central functions performed by the TTO is the scientific evaluation of disclosures submitted by academic inventors. The evaluation determines a technology's viability to be protected and licensed. Employing their scientific expertise, licensing officers begin a rigorous prior art search that reflects a particular invention against the existing IPR base in related fields of application.

> "The second thing we would do is an exhaustive search to find out the novelty [of the invention]. If at that stage it proves not to be novel, meaning we have found very, very similar work in the public domain, then we will meet with the inventors and bring our findings to their attention and try to understand whether they can come up with ideas to circumvent the prior art. If they agree, yes, this is prior art I was not familiar with, and really has no additional ideas how to change the invention to overcome the prior art, then that is the end of the case at that point. It is not novel, we really cannot protect it. [...] The next category would be that the prior art search we did finds that there is some aspect of novelty, but there is considerable amount of similar work already published or patented by others that limits the scope of the commercial applicability. Then, too, our findings will be shared with the inventors and [we] try to get additional ideas from them. Sometimes they might say "Oh, but there's a subtle difference here, I can treat my research in this way and get additional or better data", which, then, we will wait to get from him. Or he might say that "I have

> some other ideas for applications, so let me do the research for an additional six months and I'll provide you with that information." In some cases we might wait. In some other cases, depending on how big the scope is, we may file what we call a provisional patent application, and that protects what we have got up until then for twelve months. [...] The third category [...] is the top category where it looks terrific, the invention looks terrific. It's completely novel and we will definitely pursue it, even though we have not talked to any industry, but it is perfectly novel, we can get reasonably good patent protection and scope, research is ongoing at the inventor's lab, and hopefully whatever we have can be enhanced quite a bit tomorrow. As of those, we immediately decide to pursue the patent application or the patent protection, and then we will contact industry [...]."
> – *Director of the TTO of a private university* –

Here, in-depth understanding of the given technology is paramount, as the decisive differences to existing and protected technologies as well as applications thereof can be minuscule. Again, parts of the entire IC base of the TTO are activated: The scientific knowledge of licensing officers (HC) is complemented by services from external law offices that specialize in IP protection and support in the prior art search (RC). Structural capital (SC) that supports and facilitates the evaluation process is employed in the form of accessible technology databases and regular meetings that facilitate the detection and diffusion of case-relevant knowledge among single licensing officers that can then be designated to matching cases.

> "We get 500 invention disclosures a year. So, that is 10 a week. The receptionist or sometimes [...] the office manager [thinks:] "Who do you think should take this case, is it what Tom does. Or is it chemistry, it looks like chemistry. Martin does software, it looks like software", so they get distributed to the people. The clerical people are handing them to the licensing officers. And if it is not likely, it gets fixed at the Wednesday meeting: "No, *I* really should have that one, because *I am* working on X" or "I don't really know anything about this, it looks like software but it is really biology". Then you just go round the table with 30 people, if anybody has anything to say they say it [...]."
> – *Director of the TTO of a private university* –

The precise positioning of disclosed inventions within the relevant technology enables the evaluation of the inventions' potential to be protected and, ultimately, to serve as a potential base for profitable business. The decision to proceed further with a given innovation is based upon this evaluation. A very limited freedom to operate in the technological dimension can be argued to entail also a limited freedom to operate in the commercial dimension, which lowers the value of an invention. Thus, the positioning of inventions constitutes a central TTO function that adds value to the technology transfer as a whole.

Another cornerstone of success in keeping up a steady stream of disclosures from faculty is to provide them with high quality support services in all IPR issues that relate not only to their possible ambitions as entrepreneurs in spin-off companies, but also to their work in academic research in its entirety. Building and sustaining

a reputation of being the one that is able to solve problems quickly and reliably in all IPR related problems is key in maintaining long-term relationships with faculty that are the vital origin for emerging technology.

> "Ok, think of us as having two sets of customers. First set is the faculty. And if they are not happy, we never get to deal with the second set. And the second is the external business community. [There are] probably two, three things that keep your faculty happy. [...] The first is responsiveness: Answer the phone, respond to the email and don't let them move your office from campus. It is very important that faculty can just walk in here between classes. A number of Nobel laureates have sat on that couch. So, I would absolutely insist on that. [...]
> Second, smart people, bright people. The faculty are naturally trained in ten minutes, five minutes to figure out whether you are smart or not, because that is their job. And it makes a big difference even if they start with the assumption that all university administrators are idiots, if they can get their mind changed in ten minutes. So, it is important to have bright people.
> [...] And then competence. Have them know that you understand them, get the job done. If there is a delay, it is an intelligent delay. It is kind of like when I went to engineering school here. You might get every single problem set wrong and still get an A, if the mistakes were intelligent. If they were dumb, you got a zero. And it is that kind of, that they are dealing with competence. So, that is probably how we deal with the faculty. We understand that we put the academic priorities first, that we listen to them, that we know what we are doing. And the point comes when they come for your advice, not just to do what they want you to do, you know."
> *– Director of the TTO of a private university –*

As their foremost focus and career interests are mainly in academic objectives, the downside of not participating in commercialization efforts is in general rather low among faculty. Thus, should the TTO once suffer a blow to its reputation as a service institution, word rapidly spreads out among faculty with devastating effects on disclosure rates. Repairing a once damaged reputation is cumbersome. Services requested by faculty are too numerous and situation specific to be catalogued here exhaustively, and it is not even necessary for the lesson to be learnt.

To give a few examples, however, one might list the acquirement of material transfer agreements from third parties, the negotiation of sponsored research agreements in cooperation with the university's contracts office (if it is not merged with the TTO), solving infringement suspicions concerning research conducted by fellow or competing scientists, providing live support in questions concerning commercialization and "getting the job done" fast and effectively in all cases, in which faculty is enthusiastically engaged in promoting their research to be commercialized. Here the quoted term "getting the job done" is to be understood as a reflection of the necessary emphasis on being responsive and closing deals as opposed to one on risk avoidance and detached administrative tasks in the background:

"It can be anything from the world's most thankless task, which is incoming material transfer agreements:
"Get me my material", they want.
"But the company wants some mortgage on your first born", [we respond].
"Get me my material! "
"Are you sure you want to give your first born away?"

[Other problems can include the following:]
"Guess what? I have this company that wants to sponsor my work in this," [says the faculty].
"Yeah, but your background patent in that is licensed to your company. How are you going to deal with it?"

It can be:
"My grad student thinks he is the inventor and I don't think he is."

It can be:
"I'll take my company and work in my lab and do such and such..."
"No you can't, here's the conflict of interest rules."

I have one now where people were sponsoring research and saying to the researchers:
"We want you to do it in this way", and the researchers were saying:
"It won't work that way." And they are saying:
"But we're paying the money." And the researchers are saying:
"But we are not a job shop."

[...] Or I can have a professor call me up and say:
"This other professor at university X is infringing my work."
"What does that mean, why do you care? And I can't do anything about it and here's why."

Solve problems, basically. Solve them and let them get on with their work. We do not know what is going to happen, but there is millions of dollars at stake. But we will figure it out. You cannot imagine all the stuff. You cannot tell what the problems are going to be. You cannot invent what happens."
– Director of the TTO of a private university –

"I think one of the key ways to fail that I have seen too many times is that you fall into the bureaucratic mindset, you know, "My job is to move this piece of paper". That I think is the ultimate failure of a tech transfer office, whereas the ultimate success is you are a valued member of your local business community. To me those are the two ends of the spectrum. If you are just viewed as a bureaucrat then forget it, then you have failed. If you are invited to serve on panels, people are seeking you out for business opportunities within the university, then I think you have succeeded, and it is all these things working together. In the end it is your reputation, it is your ability to have repeat positive relations with the people who are going to make things happen."
– Assistant Director of the TTO at a public university –

An exhaustive list of every-day services provided to faculty is not even necessary to crystallize the TTO functions' added value to the technology transfer as a whole. By providing responsive help and support in questions and tasks that

are not in the traditional sector of responsibilities and capabilities of faculty, the TTO brands itself as an easy to approach interface between the academia and the commercial world, and, thereby, further lowers the faculty's inertia to initiate and participate in the transfer of technology. Solving concrete problems for faculty is also a very tangible and pro-active contribution to clearing obstacles out of the transfer process's way.

Another value adding set of support services are linked directly to one of the central stipulations of the Bayh-Dole Act. The act requires the university to give preference to small businesses when licensing technology. This has resulted in the active promotion of university spin-off companies, in which the academic inventors are involved to varying degrees. While the TTO does not interfere with running the start-ups as businesses, it often provides valuable services to the inventors in pre-start-up stages. The degree of involvement in helping a start-up on its feet depends very much on the case, even in our smallish sample. While some TTOs follow a *laissez-faire* strategy and leave issues of business formation entirely in the hands of the inventors or surrogate entrepreneurs, single TTOs representing another extreme may be very actively involved in organizing the establishment of the business by securing financing, constructing a management team and establishing the organization of the start-up.

> "We do not incorporate the company for [faculty]. We tell them where to go and what people have to sign up and make the payment, and they do it by themselves. In the past, we have had some [business school] students select a few projects from here to write business plans, so they have had some interactions with groups of [business school] students and, of course, entrepreneurs, because our faculty member cannot be the CEO."
> *– Director of the TTO of a public university –*

> "We do not formally assist in pulling in the money. We try to make introductions and let things go where they go, because the best persons to talk about the start-up are the entrepreneurs themselves. Eventually, I have the license to that start-up, so those people, who are part of that dance, will be sitting on the other side of the table when they come to negotiate a license. So, you know, I want our technologies to plunge, so making an introduction or two will help that, but I cannot get too involved, because, in the end, a start-up is not our property. The patent is our property that would be licensed to the start-up."
> *– Assistant Director of the TTO of a public university –*

> "Certainly we could put people in contact with VCs and angels, but basically it is none of our business - until recently, when we started to put companies together. Then we would do it all, the first couple of steps we would do everything until a VC, an owner, would come along and incorporate. Then the responsibilities would go to that person. But certainly, for start-ups we can [...] give them intelligence especially after they form. We know other IP is coming through this office that might be of use to them. [...] What we want to do now is to be much more at the front end of the formation of the companies, because we get so much more of the founder's stock. We get a bigger chunk of it, and being more of service to the faculty member, and that has happened in a few instances over the past year, where we have gone to a faculty member and [seen] what the technology looked like, it was a

good start-up situation, and so put together a business plan and then went out and sought entrepreneurs and money."
– Director of business development at the TTO of a private university –

More subtle approaches closer to the average degree of involvement include support in writing a business plan or in preparing presentations to investors or entrepreneurs interested in taking the commercialization process further.

"In two or three cases, the faculty member did everything. In almost all the other cases we played a sub-role. The role starts from helping out with making the presentation. This is something we used to do; we have not done it for the last year. We would invite a group of venture guys or angel investors and we would have five or six faculty members lined up. Each one will be making a 20-minute presentation, and those presentations are very focused on what is the significance of the science, what are the applications, where is the market and the business preference."
– Director of the TTO of a public university –

Preparing business plans and presentations necessitates a conversion of the scientific insights related to an invention into commercially selling concepts, which establishes the TTO as a converter, metaphorically speaking. Moreover, leveraging its ever-growing network of diverse actors necessary in commercialization, the TTO actively introduces the inventors to potential partners in finance and management circles in an attempt to bridge the often rather wide distance between the respective networks of the academic and the partner. Bringing the inventor and the necessary partners together is essential, because the TTO cannot replace the inventor as the ultimate expert in the respective technology.

"And to be honest, it is highly technical work. It is a wide variety of technologies that you deal with. You have to know enough detail to understand the important parts, but you cannot become the technical expert, that is the faculty member."
– Assistant Director of the TTO at a public university –

"We had some problems with people [TTO staff] with PhD degrees [...], because they loved the science, and they are trained to look in great depth in a particular area. We had to let this one person go, because [...] they are always over in the lab, learning in great detail about their inventions and science, they want to go to technical conferences to be on the cutting edge of the science and, as I tell our people, as long as you have the active involvement of the inventor, you do not need the depth and technical knowledge. If there are any technical questions, the inventor will respond to them."
– Senior Associate of the TTO of a private university –

Since technology consists much more of the tacit knowledge inherent in the inventor than the respective patent, which basically is merely a paper document assigning rights to the use of the technology, its successful transfer inevitably necessitates the personal interaction of the inventor with those promoting the business

at some stage of the process, be it as an active member of the staff or management or in a more passive role on the scientific advisory board. Thus, providing the right connections can be argued to be of great value to the outcome of the transfer. Here again, the TTO earns itself the appellation "catalyst", as it actively initiates a reaction between two or more "reagents" that self-sustainably continues towards final commercialization.

The last, but not the least by far, of the value adding services provided to faculty in this non-exhaustive review is the mediation and conversion of feedback from the industry to the inventor. Technology specific feedback collected from the industry in the early phases of marketing efforts is mediated back to the inventor who then can make necessary modifications to the invention. The modifications are presented to the industry again for further comments or closing a final licensing deal. This feedback loop is somewhat at odds with the traditional, linear view of technology diffusion as modeled, for example, by the Schumpeterian invention-innovation-diffusion trilogy (Schumpeter, 1939). Rather, it is evidence of the non-linear nature of the diffusion process.

For the purposes of gathering relevant feedback to a given technology the TTO must have a large and diverse enough base of relational capital. Understanding the feedback and converting it from industry back to the inventor is facilitated again by the TTO's strongly inter-disciplinary human capital, as well as supporting structural capital in the form of contact- and cross-related, invention-specific tracking databases. The intrinsic value in this TTO function lies in the facilitation of finding or, better, affecting a match between scientific discoveries and market need-based solutions.

7.4.5 Value adding functions in the interface of the commercial world

The commercial world, epitomized either by individual companies or entrepreneurs looking for a technology to base a business on, is served and cooperated with by a set of functions very different from that provided to the academic world. Although many of the functions provide output that is (I can't help thinking of the Dynamic Duo when this word is used) fed back towards the academic world as input (e.g. the industry feedback touched on earlier), they are treat here in a more isolated manner for clarity's sake and in an attempt to minimize repetition.

Looking from the perspective of any newly emerging technology, marketing related activities are probably among the first that initiate contact towards the industry. While cold-calling potential customers is an indispensable and frequently

used method in the attempt to make new contacts, it is not necessarily the most effective or the most popular one among the TTOs interviewed for this study. As a more focused and strategic way of marketing new technologies TTOs heavily lean on their existing relational capital and the contacts that comprise it. Surprisingly, very many of the contacts are provided by the particular inventors.

> "So, as you have probably been told before, it is the actual investigators that have developed and disclosed the technology that often they are a major player in building the network and the contact base. Not always, but they are certainly an important factor. They have their own network. That being said, we encourage them to attend conferences, people read their papers, they get contact... So, often that is the first place you go to ask "Do you know anybody or industries, or fellow researcher that have companies that have an interest in the technology that you are doing?", because they know the field best."
> *– Director of the TTO of a public university –*

Established partners within the existing relational capital base of the TTO or the one of the inventor are well known and familiar, which is a valuable asset in finding a compatible customer efficiently for any given technology, because search costs are comparatively lower than when cold-calling. In existing relationships, organizational procedures and guidelines are also well known, and personal ties have already been formed, which mitigates costs related to setting up functioning communication.

If a suitable, interested customer is not to be found among the relational capital of a TTO, it can be used as an indirect link in the search. All of the actors comprising a TTO's relational capital have their own relational capital that can be accessed through recommendations and suggestions. Existing TTO customers, for example, know their own industry's other actors fairly well and are able to pinpoint those that might be interested in the particular technology marketed by the TTO. With every new contact forged the relational capital of the TTO grows and can be efficiently leveraged in future.

As already elaborated on above, obtaining feedback that can be channeled back to the inventor also constitutes a major objective of marketing. Each time a contact (RC) provides relevant feedback (HC) of any kind on the marketed technology it is recorded in the case specific tracking database (SC) and forwarded later to the inventor who then can utilize it to modify or develop his invention further. The feedback provides a mechanism that facilitates the matching of scientific endeavors with market needs:

> "The marketing process is not only to find an interested party who will take a license, but also to get feedback from the private sector: *"This is what we have, tell us what advantage you see of this technology, and if you don't see any interest from you company for this technology, do you know others, who may be doing something similar that they might have an interest in?"* It is

really to get their feedback as well as to find out if they are interested. Not always does their feedback help us. By that I mean, we always share all the feedback that we gather with the inventors. If the feedback is negative, then many times our inventors do not want to accept it, or do not want to believe it, but in the process, though, inventors may come up with a different way of doing things, or may come up with a different idea that they did not think about before. It helps both parties quite a bit. And because we have this dialogue, we can come back to the same people within the same industries with other ideas, because during this first dialogue they might be saying: *"But in the event you have something along those lines, contact us"*. That is how the networking gets expanded, and the feedback we collect is also very useful for our inventors."
– Director of the TTO of a public university –

In summary, one might say that transaction costs in general are lower and the probability of finding a matching customer is higher when existing relational capital is leveraged in the marketing of technologies. Marketing efforts and the maintenance of the feedback loop requires the exploitation of a TTO's entire IC base. The relational capital base serves as a channel through which the TTO can leverage its human capital and bring it to bear efficiently. Again, interdisciplinary human capital fusing scientific and commercial expertise in single individuals is key in identifying potential customers. Identification is based on the evaluation of compatibility of the marketed technology with customers' existing technology bases and the technology's suitability to the customers' business logics.

Thus, the licensing officer responsible for a case must have the necessary science- and business-related skills to be able to make such an evaluation. Moreover, the interdisciplinary knowledge is needed to, first, convert the mainly technical specifications of the marketed technology, as provided by the inventor, into marketing jargon emphasizing the business solutions the technology is able to support, and, second, to convert the feedback provided by the market contacts back into technical specifications that the invention would have to meet before a customer is truly interested in licensing it.

"I need to be able to not become glassy eyed when I talk to my inventors and they discuss their invention, because it is all going over my head. I need to be able to grasp the essentials and be able to articulate those to a potential licensee. Otherwise I am not helping my inventor. They are doing the work, so I need to be able to save them time that way. I translate the hardcore technical document that the inventor provides. It gives all the details. But it is all the details; it is not a concise, digested presentation of the features and benefits. Can I give an elevator speech, the usual venture capital elevator speech on this technology? I have got to be able to do that. A technical background helps me do that. Especially in a way that does not put all of the burden back onto the inventor."
– Assistant Director of the TTO at a public university –

Structural capital in the form of databases keeping track of case specific details in terms of contacts, recommendations, dialogues, requests, demanded specifications,

etc. and regular TTO internal meetings through which relevant human capital is allocated to cases supports the marketing functions.

> "And then we have this rather extensive database system that has been carefully involved over several years that contains... there is a contacts list, I think we have over 5000 people on the contacts list, companies or whatever. [...] If you want to go and search for by company or by keyword, technology keyword etc., [you can do that] both for companies and individual contacts. Each docket, each invention has its own file docket, where all the information is inputted, and as I said, that is being made accessible to the inventors, they can check if they have any questions about their invention that what is happening to them."
> *– Senior Associate of the TTO of a private university –*

In terms of value creation, these functions actively contribute to establishing the vital bi-directional bridge to the commercial world through which technology is diffused, and encourage the active involvement of the industry in the transfer process.

While marketing is an active function aiming at tying the commercial world into the transfer process, TTO-managed electronic technology databases, also called technology portals, displaying all technologies available for licensing at a given university provide an easy to approach public interface that, while being a more passive mechanism, nevertheless is applied as a major channel in outreach activities by all the offices interviewed. Provided with summarized descriptions and all relevant information, each technology is accessible to the public through the Internet. For companies on the search for new solutions and technological opportunities such an interface is of value, as it decreases search costs significantly. Being a complementary mechanism to marketing, a well-maintained IPR database maximizes the visibility of available technologies and thereby enhances the probability of licensing.

> "There is a database in our central office where a company [...] can go in and inquire about technologies, or inquire about research capabilities and enter their interests. [...] that inquiry is sent to someone who then will contact researchers working in that area and ask if they are interested in performing a research."
> *– Director of the TTO of a public university –*

The interface also provides a number of positive externalities that have favorable indirect effects on the technology transfer process. To mention one illuminating example, an exhaustive and easy to access technology portal serves as an indicator for the types of research conducted in the laboratories of the respective university. It is a major facilitator in attracting industrial sponsored research funding to the university, because single research groups are, thereby, easily found and approached by companies looking for academic research alliances.

In establishing and maintaining such a database, employing the IC of a TTO in its entirety is necessary again. In this case, the role of well-functioning structural capital in the form of database structures is emphasized, while interdisciplinary human capital is essential for extracting and converting the essence of each invention into content inserted into and displayed through the databases. Relational capital is implicitly involved, as the whole system is built for the purpose of attracting, serving and connecting to new and existing partners.

Once marketing as well as other outreach activities have fulfilled their purpose and an interested customer is found, the TTO and the licensee-to-be negotiate a license. In this phase value is added by the TTO mainly in two ways. First, applying its human capital in the form of experience and skills in negotiating contract terms, on the one hand, and utilizing the results of both the scientific and commercial evaluations of the technology to be licensed, on the other, the licensing officer can ensure that the terms of licensing and the entailing compensation paid by the licensee correspond to the real value of the technology with a higher probability, than if negotiations were lead by the original inventor.

In the light of pure economics, it might be argued that, in the short-term, licensing negotiations are a zero sum game with the total social benefit being constant independently of its allocation between the licensee, the university, the TTO, and the inventor. In the long run, however, licensing deals unfavorable to the inventors diminish incentives to disclose and participate in commercialization in the first place. Thus, the value inherent in the TTO's negotiation function finds expression not only in a relatively superior influx of royalties, but also more importantly in sustaining the fundamental prerequisite of technology transfer, the constant inflow of new technology from the academic laboratories to the TTO.

> "But you also have to have negotiating skills. You really have to be able to see the other side and the kind of... it is negotiating that is more like diplomatic negotiation than negotiating the price of a car, because you are going to be living together for a long time. It is not some zero sum game of how much I am paying for a used car, that is it. There are a lot of things you need, they need, and it is two different cultures that you have to explain to each other. Which is why the industrial experience benefits us so much, because we are hiring bilingual people. They have an academic background and they understand how industry thinks. [...] They have to feel that even though you are on the university's side and are negotiating for the university's benefit that you are fair that you can creatively solve problems [...]. You do not have to win in a negotiation. But instead see the victory in getting a fair deal done."
> *– Director of the TTO of a private university –*

The second value providing function in the licensing phase of the transfer process has to be reviewed in the light of the TTO's stated mission, which emphasizes the importance of public benefit as the objective of university technology transfer. As will be elaborated on shortly, purely profit maximizing objectives are

hard to justify in university technology transfer. They are just one aspect of the entire mission and, as such, are pursued mainly to complement research funding up-holding the universities' academic mission. What was stated as more important, regardless of whether the university in question was public or private, was that the given technology was put to use in society in the first place. Though being a rather broad agenda, making efforts to see a technology developed and diffused entails a number of very concrete measures.

A fair number of these measures is laid down in the form of stipulations for TTOs in a public initiative publication authored and signed by 12 major US university TTOs called *In the Public Interest: Nine Points to Consider in Licensing University Technology* (available at www.autm.net, last accessed on December 13th, 2007). Among other things, the stipulations prompt TTOs to design license agreements in a way that allows the office to "reserve the right to practice licensed inventions and to allow other non-profit and governmental organizations to do so" (p. 2) so that performing and publishing research related to the field of the invention is not constricted unnecessarily.

Moreover, license agreements that provide the licensee with exclusive rights to an invention are encouraged to include clauses that demand the development and use of the underlying invention by setting milestones that need to be met or including the obligation to give sublicenses to third parties that aim to fulfill unmet market or public health needs. In general, exclusive rights should be reserved for cases in which "significant investment of time and resources in a technology" are required to develop and widely implement it. In particular, inventions in the area of research tools should be kept widely accessible. Again, exclusive licensing is discouraged due to their potential negative impacts on unanticipated uses, further research, future commercialization efforts and markets.

Also the unnecessary licensing of "future improvements" of existing licensed inventions is to be considered carefully in order to avoid enchaining the inventor's research program to the licensee. This could strongly restrict the inventor's ability to obtain industrial and other research funding and to collaborate with colleagues working for other companies.

According to the stipulations, special attention is to be paid to licensing to "patent aggregators". Aggregators operating according to the "value added" model gather coherent and comprehensive IPR portfolios from many sources around single technologies. In doing so, they are in the position to provide themselves or secondary licensees with a great freedom to operate. As universities do not have the capability to assemble such portfolios, "value adding" aggregators are argued to "serve an important translational function in the successful development of new technologies and so exert a positive force toward commercialization". In contrast,

aggregators operating under the "patent troll" model are the pitfalls to be avoided at all cost. Trolls strive to obtain rights that slash widely across entire technological fields without intending to develop the respective technologies themselves but to strongly limit the freedom to operate of other actors. When owned by trolls, technologies and their development are kept inert as they only play a strategic role in the troll's actions. Any actor aspiring to operate in the technological vicinity of a troll is forced to sublicense from it.

A final stipulation reviewed here comprises the inclusion of provisions in agreements that attend to special societal needs such as the therapeutic, diagnostic, and agricultural needs of the developing world or patient population too small to be of interest to commercial ventures. Basically, these provisions aim at ensuring that these markets have access to relevant technology at low- or no-cost. As an illustrative example, one of the interviewed TTOs not only donated the rights to one of its therapeutics technologies addressing an orphan population of patients to the respective central association for the underlying disease, but it actually provided financing out of its own proprietary funds to develop a prototype of the therapeutic instrument that was later used in the treatment of the disease.

In a cynical world, in which the "educational industry" has become ever more competitive and incentive driven, one might wonder where the motivation for universities lies to diffuse technology at all cost. This is a question that this study is unable to answer definitively based on empirical evidence. Consulting the contents of the Bayh-Dole Act provides only an ambiguous answer, as it only requires the active facilitation of commercialization of inventions and the preference for domestic and small industries, not their diffusion at any cost.

According to our underlying data, it is simply the task of an educational research institution to create and diffuse knowledge, as well as to deploy inventions thereof, to society with profits and costs not being priority criteria in the process. But when resources for the primary functions of research and education are limited as they always are, why should universities allocate them to a function that does not necessarily provide any additional resources but might even produce losses? How does a single university's research and education benefit from dissipating its seed if the fruit is enjoyed by others? The question is of special interest in a setting where completely public and private universities co-exist with each other having different incentive structures.

It is the view and argument of this study that for a university's reputation as well as its impact in the academic world and, thereby, its capability to attract faculty and students of high quality, profits and other monetary indices are rather irrelevant, as they do not convey signals of academic merit or the standard of research and education. Rather, being able to point out the number and, especially, the impact

of technologies that have emerged out of a given university make a decisive difference. Take Yahoo! as an illustration. Being conceived by two Stanford University students in their spare time, the company has become one of the most popular brands and services for a great number of years . As the students used their own resources, Stanford University did not have any rights to the algorithms used in running the portal. Nonetheless, Yahoo! has benefited Stanford greatly, because the credit for developing the necessary capabilities and the students' entrepreneurial drive are credited to the university and its progressive education.

We argue that breakthrough technologies with impact, not the revenues created by them, are important signals carrying information about a university's standard and quality and provide, thereby, an important edge in the competition for key faculty, students, and a rank among top universities. As stated by one of the interviewees:

> "When I was at school [X], there was a number of potential faculty that were looking at positions at the medical school that actually came in and interviewed the licensing office as part of their own due diligence for accepting a position."
> *– Director of the TTO of a public university –*

Thus, one could argue, universities have also strong internal and strategic incentives to maintain TTO operations with the ultimate goal to diffuse technology as broadly as possible.

As the last value adding TTO function reviewed here, monitoring closed licensing agreements is an essential requirement, as the strength of the protection of IP is equal to the credibility of its prosecution. While clauses included in license agreements for ensuring a fast and broad application of the technology have effect only if met, the prosecution of infringements and non-compliance is still not a straightforward issue. Prosecution is not recommended if no direct benefit is to be expected in the light of furthering the transfer process, because involvement in lawsuits never reflects well on any of the parties involved. Prosecution might do more harm than good in the long run in cases where an infringer is a great contributor of industrial sponsorships to the particular university's research.

> "[...] he had this idea, he said: "[With] *the semi-conductor* [industry] *we are having great difficulties licensing, and companies are very persistent and don't want to have licenses. So why don't we pool our inventions in that area, and then hire a law firm to enforce these patents* [...] *and threaten to sue if they don't* [license]." And I said: "*That's the worst idea I have ever heard in my entire life, because these are companies that are bringing in tens of millions of dollars into the interdisciplinary research center* [...]." It is a good example. You need to look at it in the context of the university rather than just the office itself and what is going to get the most money to the office."
> *– Senior Associate of the TTO of a private university –*

Concluding the analysis of the value creating functions of TTOs, three issues have to be addressed before continuing with the brief discussion of monetary indices of value creation.

First, in reality TTOs perform a plethora of functions that add value in many different forms in many different contexts. For the sake of conciseness, the discussion of functions in the above section has been limited to those that are the most focal from the perspective of technology transfer One such example of functions not elaborated on in this paper is the support that a TTO often provides internally to other university departments, such as procurement or contracts offices in all IPR related issues, or the indirect effect that the sheer presence of a TTO of renown has on a university's ability to recruit better faculty.

> "So we have a good relationship with the office of contracts and grants, because it is right upstairs and handles the intake of research. The great proposals go to them, they send them off and they manage the whole proposal and research contract aspect, both with the government, and with the private industry. Those often have intellectual property terms, certain commitments for licensing, and so we get involved with that. We have a good relationship with them, we are support to them. Similarly for purchasing. Purchasing will buy things, let us say they are going to in-license some software. The software maker says: *"Okay, I'm going to give you a 90% discount, but I want some feedback."* If they do not work the description of feedback correctly, it could get to the realm of patents and things like that. So, those sometimes pull us in. Not as often as the contracts folks, but they will pull us in, if intellectual properties are an issue with their purchasing agreements. There is a drive to get a new institute on campus. We are going to pull in some money, set up a new institute. They will pull us in to talk about intellectual property and how that would relate especially to industry sponsors. So internally, yeah, there is a lot of interaction that occurs. We work with the campus council office quite a bit. In our world litigation occurs. Litigation tends to have a 4 to 5 million dollar price tag. So that is a big impact on the money. So in those types of things the chancellor would be interested, the budget office would be interested, because that is a significant amount of spending."
> *– Assistant Director of the TTO of a public university –*

Yet other positive effects of TTO activities are touched on in the following:

> "The real value that I think we create is the new relationships that result from this activity, from which can come consulting opportunities for faculty, sometimes, or students. Hiring graduating students, sometimes they want to hire especially their co-inventors. They sometimes provide sponsored research support, or sometimes start-ups and small companies will have the inventors on their boards and scientific advisory boards for which they get some kind of compensation. Sometimes we even see donations [from well-served inventors that have done well in commercialization]."
> *– Senior Associate of the TTO of a private university –*

Second, procedures and ways of working described in this section represented generalizations thereof. Single TTOs may vary in many aspects in their actions. Those functions are included in the above treatment that, on a general level, coincided by

and large with all interviewed TTOs. Thus, deductions should be made with care and awareness of the underlying generalizations.

Lastly, the explicit treatment of IPR protection via patenting, securing copyrights or registering trademarks as a TTO function has been purposefully omitted. This is not to say that it is notimportant as a value creating function of a TTO. On the contrary, it is probably the most central of functions. Without formally and legally securing the rights to an invention there is nothing to transfer. Thus, IPR protection is a prerequisite to any kind of transfer of technology; it is an axiomatic step in the process. With this having been said, an in-depth elaboration of IPR protection is not necessary and does not provide much new insight or contribution. It is a mechanical task. Suffice it to say that the TTOs interviewed for this study, without exception, revert to specialized external law firms in drafting and prosecuting patents and the other forms of IPR protection once the prior art search and the commercial evaluation of the invention approve protection. In doing so, the law firms cooperate with the inventors directly to capture the essence of the invention and the novel aspects thereof.

Before engaging in the discussion of implications, first a brief treatment of monetary indices that have served as more traditional measures of value creation of TTOs in past literature. They are also the platform, based on which much public and academic criticism has been voiced against the real impacts of the Bayh-Dole Act. In the light of such criticism, the relevance of these indices has emerged as a rather strong discourse from the data, and, thus, they deserve a separate treatment of their own. Moreover, the omission of monetary measures of added value from the discussion, especially when assessing the impacts of government interventions that are commonly evaluated based on macro-economic, quantitative indices, would leave a void in the coherence of the analysis.

7.4.6 The relevance of monetary indicators as proxies for value

It is interesting to note that, against the expectations of the layman, in the general mission statements of TTOs income accruing to universities through licensing royalties or equity was never ranked to be of high priority. In some cases generating licensing income was mentioned as one of a number of objectives of the TTO in officially published sources such as the offices' Internet sites or promotional print material. In the course of the interviews, however, the objective of income generation was systematically de-emphasized in relation to objectives treated earlier.

It is surprising at first, because revenue streams are probably the most tangible and quantifiable dimension of value, as they concretely measure the volume and

outcome of economic activity in so many other contexts. Ultimately, however, the reasons for not focusing on revenue streams as a measure of created value are manifold and evident:

> "Well, I think the monetary thing is a canard. First of all, statistically you got to get lucky before you make a lot of money. Secondly, most people think that they can play and they get lucky. If you could do that, it would be much easier to buy a lottery ticket than to do the kind of work we do. As you look across the country, there are a few universities that have picked the lottery once in a while and made a significant difference in the fortunes of the university for a while; but not very many. So, there are so much false expectations about the money [...]. If you set up an organization with unreachable goals, unless you get lucky, and with the thought that you are going to run it primarily with financial benefit when that is not how it works, everyone is doomed to unhappiness. [...] This year the gross income, and people always forget that gross is not net, is going to be high, about 60 million. Almost 40% of it is due to one invention, but at least it is 40%, not 80%, as it is in so many universities that get lucky. And it is continuing royalty income rather than a single piece of equity. So it is nice to have. Gross income, when we pay inventors, pay co-owners, pay expenses and pay for patents, if we calculate what is going to the general fund and the departments together, it will be about 25 million. Which is nice, but [...] our budget is over a billion dollars in research, we are probably a 1.3 billion dollar operation, so 25 million is 2%. It is nice, because it is discretionary funds, but it is not going to change the economics of this institution."
> *– Director of the TTO of a private university –*

> "You will see that any office bringing in more than 10 million, 96% to 98% is due to one or two, and the rest of them, collectively, would be the other hundred or two hundred [cumulative] deals [...]."
> *– Director of the TTO of a public university –*

> "[...] when we had our venture appreciation party a year or so ago where ventures generating over five million dollars were recognized, there were 12 of them, and we had to confess that out of the 12, six of them we did not think worth anything when they were first disclosed to us. [...] That is the problem. Everyone in this office has been through this. Things we said: *"Oh, this is the greatest invention ever, it can't possibly fail. This is really..."* and it has gone nowhere. And there have been other things, we have just shaken our heads and said *"What's this?"* and then it ends up for whatever reason being very significant. It is hard to say. But it is as I said, we need the portfolio, we have over 400 things, anyone of which... let us say 4 of those are over a million [annually] [...]. It is just too many unknowns and typically it is a long development cycle, so..."
> *– Senior Associate of the TTO at a private university –*

Pure revenue streams seem to be an unreliable measure of value creation, as the commercial success of a technology is unpredictable before its market introduction. The implication is that creating significant revenues is a numbers game, a matter of "getting lucky". Doing things right does not guarantee commercial success due to the technological and market uncertainties inherent in early stage technologies that universities mostly license. In this respect, revenues do not reliably measure value created by TTOs, as the ultimate commercial success of a certain technology

is not necessarily a function of TTO activities but of the commercial potential of the technology itself, its viability on commercial markets, and the actions of the entities commercializing it.

Another reason to dismiss revenues as the dominant driver behind TTO actions is that they often pale in significance when set in relation to overall budgets dedicated to research at universities. The contribution to research budgets is marginal, even when annual TTO revenues are among the highest in the country. Thus, maximizing profits by focusing only on those transfer transactions that are expected to reap the highest payoff might compromise the transfer of technologies that could potentially show great social or human impact when put to use.

There are still other reasons not to place major importance on revenue streams or other purely quantitative measures as indicators of value creation:

> "You cannot focus too much on revenue for a lot of reasons. A deal that brings in a hundred dollars may be very meaningful to the faculty member who submitted that disclosure and just went through the process. Whereas the homerun that is pulling in millions of dollars royalties a quarter, that is going to get a lot of attention. But they are the homerun; you cannot always count on them. So, for a well-balanced office you hope for that homerun, but if it does not show up, there are a lot of other things you can point at to show that you are a successful office. [...] And your top one or two [inventions] are probably going to be 50% [of gross royalty income]. It is a homerun game. But, to make the faculty happy, if you only focus on the homeruns and only serve the people who might give you those homeruns, you are only serving a small percentage of the faculty, and the rest will be pretty unhappy and you are not running a good office."
> *– Assistant Director of the TTO at a public university –*

To run a TTO in a "well-balanced" way a revenue-generating license constitutes a valuable resource. As part of the income is retained by the TTO as discretionary funds, royalty and equity income provides the TTO with more autonomy and a greater freedom to operate financially, because resources do not have to be applied for through the rigid and bureaucratic channels of the university's administration. Nevertheless, it is merely seen as a resource from that perspective, not an objective *per se*.

On the other hand, a license, regardless of whether it actually generates revenue, can constitute value from the perspective of the faculty, as it motivates the faculty's research and provides a feeling of success. This value is immeasurable in monetary terms, as it affects the faculty's propensity to disclose future research and generate potential marketable technologies. These, in turn, constitute sources of monetary return that cannot be anticipated in the present. Thus, focusing only on revenue as a proxy for value is a shortsighted strategy. Serving only those few faculty members responsible for potential home-run technologies leaves the majority of faculty dissatisfied with the office's services. The problem is that it is this dissatisfied

majority of inventors that constitutes the base for future home-run technologies. Therefore, equal service to all faculty members is key for the longevity of a successful office from the perspective of sustainable technology transfer:

> "So everybody gets a basic level of service at the disclosures. So if you disclose an invention, we are going to come up with a non-confidential description, put it on the website, we are going to market it and we are going to see if it sticks to anything. Maybe [it generates] low dollars and maybe high dollars, but we are going to do the same basic service to everybody."
> *– Assistant Director of the TTO at a public university –*

Furthermore, depending on whether a university is public or private, focusing on revenues might reverberate negatively in the local community and damage the university's relationship with its surrounding social environment:

> "We are [a] public university. So if we focused on gross revenue, it will be too easy for those 38% of [local] licensees to say *"Hey wait a minute, we are working. All that money is coming out of our pocket* [through royalties and taxes]. *You're not helping the* [local] *economy; you're just a cash register for the university."* So we don't really emphasise that number.
> *– Assistant Director of the TTO at a public university –*

In other words, publicly financed universities with an implicit societal mission to strengthen local economies are constrained in measuring their success in terms of revenue, as maximizing the university's profits is in strong contrast to (i) the tax payers' perceived right to benefit from the technology largely generated based on their taxes and (ii) the paying licensees' expectations that their royalties will be pumped back into the local economy in one form or another. Of course, private university TTOs do not have these constraints to the same extent.

Other reasons that render purely quantitative comparisons of TTO activity less valuable include the fact that the amount of research conducted at a given university is affected by the amount of governmental research funding provided to it. This in turn translates into differences in the number of invention disclosures that constitutes the pool of technologies available for transfer. Furthermore, the field of technology that an invention is made in correlates with the amount of potential revenues that it is able to generate. As universities differ in their research foci, there are systematical differences in licensing revenues to be expected:

> "These are deals that involve financial transactions across all three ways of protecting: patent, copyright and trademark. The numbers are tied very much to the economy, they are tied to federal government funding of research. [...] If you look at the AUTM statistics, if you get two million in research funding [you can] expect one disclosure, so we get around 700 million in research funding, we should have about 350 disclosures. I think last year we had, let us see, 345.
> Some universities bias themselves. They just set up their systems so they get lots of disclosures. Others work the other way. I would be a little concerned if you are getting too few

> disclosures, because you are either, you are missing the diamond in the rough, or it is possible your faculty has lost confidence in your office. We have seen that in a couple of cases where, not here, but the disclosure numbers fall off the cliff and it is because the faculty have comforted their hands and said we are not going to deal with the office anymore.
> [...]Also when you break down the numbers, [...] the revenues will be dominated by therapeutics. [...] So in a certain sense it is not fair to judge an office on numbers alone, it is one part of the entire picture."
> *– Assistant Director of the TTO of a public university –*

Although not a measure of commercial success, the number of disclosures is an indicator, if controlled for the effects of research funding, of whether the TTO is able to create value for faculty. Mistrust in and dissatisfaction with the office will have a negative impact on the number of disclosures. That being said, disclosures can be used in a controlled environment to proxy and monitor the value generated to faculty. It is important to note that such monitoring is valuable only in the context of a single office for the purposes of charting its development over time. Comparisons between offices are less valuable due to the differences in external influences as discussed above.

Comparing measures of quantifiable value, for example, the number of licensing deals made, across universities is difficult for two additional reasons. Firstly, some technologies are more suitable for non-exclusive licenses than others. This is especially relevant in the case of platform technologies that are very broadly utilized among the appropriate industries. Licensing platform technologies increases the number of licenses by a TTO manifold in comparison to non-platform technologies with very narrow application opportunities. Thus, depending on the research foci of universities, the types of technologies emerging from research have a great impact on the number of potential licenses. Secondly, some technologies also require the bundling of single inventions to comprise a sensible and protectable whole. Bundling is an arbitrary decision, however, and should be made with the goal of optimal transfer in mind, not to increase deal flow. TTO's with internal incentive structures based on deal flow are motivated to license technology in sub-optimally small pieces in an attempt to increase deal flow:

> "[License] deal flow has always been in the 20-22 range, and part of it is because [...], with one exception, we have not had a type of software for instance that [University X] has that is not exclusively licensed to a very large number of companies, or like [University Y] has had a cell line in biological research that is so valuable to a large number of biotech companies that virtually every single company took a license to that cell line. We have not had any sort of proprietary materials or proprietary software like that.
> The other thing is [how] we count our deals. Each licensed deal is counted as one even though each one may have anywhere from half a dozen inventions to as many as 48 inventions. But we will count that as one deal and not six or 48. And we do not count as deals where a company has sponsored a research project, and in that agreement we have entered license terms. Then, when an invention is disclosed [from that project], we inform the company,

and the company is very interested in the patent rights. [In such a case] there will be no separate license deal, however, because most of the terms are already part of the research agreement, and we do not count those research agreements as license deals, because we are not entering to a separate new license deal.
[...] So, I know that different universities have very, very different criteria for doing this counting and even though we are reflected as a low number of deal flow in terms of licenses, I do not want to change it. There is a set of criteria that was established and we will follow that set."
– Director of the TTO of a public university –

With all this being said, the benefits of revenue streams generated through licensing must also be acknowledged. It is merely their role as an indicator of success and variable of comparison between TTOs that has to be scrutinized critically. To begin with, licensing income enhances the flexibility of the TTO to react quickly to emerging situations and apply its discretionary assets without having to apply for resources through the university's bureaucracy. As has been shown earlier, there are a multitude of TTO activities that do not necessarily relate to promoting the licensing process of technologies directly, but are valuable in the light of public benefit and nurture the conduciveness of the surrounding environment to successful technology transfer. As opportunities to enhance this conduciveness are unpredictable, additional flexibility in terms of resources enabling reacting to the opportunities is a valuable asset.

"Structurally we are just a department of the university that reports up the academic ladder, the research ladder. But I do not have to ask for money, because we earn enough. It increases the autonomy. We are largely autonomous when we behave ourselves. Which is, you know, do the right thing, do not get into trouble."
– Director of the TTO of a private university –

Second, potential licensing revenues not only motivate the researcher pursuing personal wealth to push forward and commercialize the work, in other words, to initiate the transfer process in the first place, but it is also an additional resource, though a small one, to the department that receives its share according to the royalty sharing policies of each university. One could argue that in the case of the wealth-seeking researcher it is the sheer possibility, the anticipation of winning in the game of commercialization that serves as the true motivator rather than the exact probability of it, as the latter seems to be rather insignificant. Finally, despite its unreliable and invalid nature as a proxy for success in the light of the broader mission of TTOs, it is nevertheless an indicator closely monitored and taken as a signal of performance by the environment:

"I do not know if you have looked at AUTM Surveys, we are in the top 15-20 institutions in the country. Last [year] we did 30 million and this year we will do about 40 million dollars.

> So from that point of view we do well with the metrics for money. [...] I would not consider money an official metric, that is one of the unofficial ones, but people pay attention to you. If you make money, people are happy; at least here. So we do make money, we are well known, we are well respected in the community."
> *– Director of the TTO of a public university –*

In the end, however, focusing solely on metrics that attempt to measure commercial success does not capture the full spectrum of value generated by a TTO. Many dimensions of a TTO's mission and, thus, value creation do not materialize in the form of commercial indicators. As an illustrative example, those offices also responsible for attracting industrial sponsored research need an array of additional metrics to monitor performance over time:

> "Well, of course metrics like that have a place. But if you are looking at the office [as a whole][2], certainly license revenue is not an adequate metric for [the office's] success. The number of licenses is not an adequate metric. They are a piece of the picture, but I think one needs to look at how much emphasis to put on those metrics, not whether you look at them, but is that all you look at? We are the research arm and the licensing arm. [...] Another metric we would use, is how many dollars go directly to research on the campus, in research groups, how much new research has been brought in? That is the metric. How many new faculties are being engaged to participate in this research? How many student PhDs are coming out of this research? Those are all metrics, too."
> *– Director of the TTO of a public university –*

To summarize, in the context of university technology transfer offices, indicators of performance such as number of patents, agreements, licenses etc. do not constitute value as such. They are mere proxies and are affected by external circumstances such as the nature of technology, the economic growth cycle, and governmental research funding. The real added value generated by TTOs is only partially and indirectly manifest in these proxies. Rather, value is added through those activities of the office that have an impact on the propensity and willingness of inventors to commercialize inventions, favor long-term public benefits that are not necessarily commercially viable in the short-term, strengthen the entire system of the technology transfer community including entrepreneurs, financiers, support organizations, etc. by serving as a nexus of contacts and providing "match-making" services, advising researchers in protecting IPR, and so forth. These activities are seldom quantifiable and have to be considered as investments in future technology transfer, because they strengthen the necessary infrastructure.

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[2] The original name of the office has been omitted for reasons of anonymity. In this particular case the office handles also industrial research agreements.

As such, indices based on annual deal or revenue flow cannot capture the value provided by a TTO, because it will manifest itself in periods still to come and are hardly attributable to any single action taken by a TTO. Another difficulty with measuring the added value provided by TTOs is that it is tough to assess how much less commercialized or otherwise diffused technology would emerge out of universities if TTOs or equivalent instances did not exist in the first place. How easily would a university inventor approach a patent office or a VC if it was not for the contacts of the TTO or the educational services that lower the psychological hurdle of scientists to approach the realm of commercialization? If the differences could be measured, one would be much closer to capturing the real added value provided by TTOs.

Quantitative indicators can be utilized to monitor different stages of the transfer process within a single TTO, however, as they confer information on the performance of different TTO functions and relationships as compared to prior periods. Therefore, they are important tools in self-evaluating the value creation process of any given office, but should not be sole measures of value creation.

7.5 Conclusions

This analysis set out to examine one of the central manifestations that government intervention in the form of the Bayh-Dole Act gave birth to – the university technology transfer office. To better understand the potential and tangible leverage that such legislation can have on the economy and society in broader terms, the specific interest was in how a selection of the most successful offices at US universities contribute to the advancement of technological progress and, thereby, carry out the agenda drafted in the Bayh-Dole Act.

Although the establishment of TTOs was not specifically mandated in the Act, it was a natural consequence of the stipulations therein. For the traditional administrative organs dealing with the university's conventional affairs, the multitude of tasks and the related expertise necessary proved a burden too extensive to handle with conventional resources. There was a need for a designated unit that could tackle the obligations imposed by the Bayh-Dole Act and could support the university in its extended mandate that now included the commercialization of research.

The true motivation for the enactment of Bayh-Dole originated in the need to standardize the plethora of different and diverging guidelines and legislation governing the ownership of intellectual property arising from federally funded research in different US states. The consequences were far broader than the sole

simplification and stream-lining of legislation. Among other things out of the focus of this analysis, the Act basically enforced the emergence of an additional and strategically dedicated mechanism to complement the existing mechanisms of university technology transfer (including education, publication, sponsored research, seminars, consulting, joint R&D, academic entrepreneurship etc.). The emphasis here is on the word "complement", because it is by no means a replacement or an alternative to the earlier listed mechanisms. The TTO is a support organization providing value adding services that close the rifts and gaps between the academic and commercial worlds still left open by these conventional methods of knowledge diffusion.

In doing so, the TTO is driven by two major factors: The mandates stipulated by the Bayh-Dole Act and the primary mandates and interests of universities, namely education and research. Thus, in their mission statements TTOs combine both the mandates of the Bayh-Dole Act with those of the universities to, firstly, guarantee the competitiveness of the particular universities in the academic world by protecting interests of their most precious stakeholders, the researchers, and secondly, to adhere to the legislative mandates by protecting IPR and promoting it to commercial use.

In the process, they implicitly, or at best, strategically guarantee the sustainability of the flow of technologies out of the laboratories towards market application, as their actions and motives uphold and sustain the incentive structures of both of the worlds, the academic and the commercial. This is accomplished by performing and specializing in the very functions that neither world has been able or willing to perform in order to take a step closer towards each other. These contributions are often hard to capture in quantitative measures, which has led to common criticism about the effectiveness of TTOs. It is proposed that such measures be used with care in the comparative evaluation of TTO performance, but also point at and recognize their value as parameters that can be utilized to internally monitor the performance of each TTO individually over time as a tool of management.

Alongside the substance-related analysis, a further contribution was made to the literature of knowledge management and IC by showing the interaction of IC components in an empirical manner, since the IC literature lacks a rich empirical tradition. The utilization of the Value Platform Model ws shown to be a structured and comprehensive framework to analyze the key success factors of organizational practices and understand the underlying dynamics of single resources. Therefore the framework, having been mainly the subject of theoretical debate, is highly applicable to empirical research. It should be emphasized, however, that such application is only feasible under considerable context-specificity – an aspect that is at the same time one of the central strengths of the framework.

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CHAPTER 8

PROMOTING EFFICIENT TREATMENT: NEW TECHNOLOGY AND HEALTH CARE COSTS

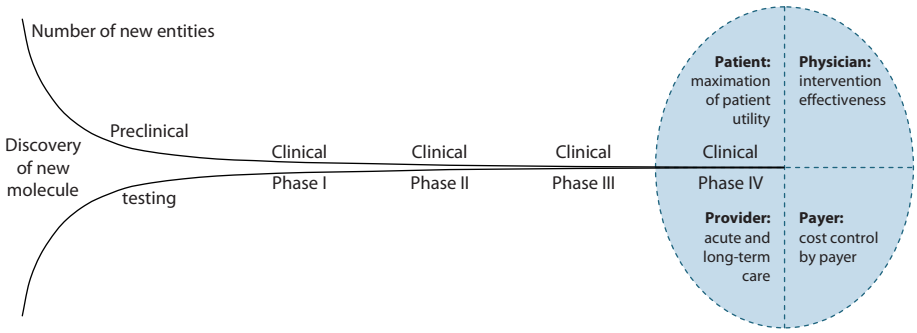
Martti Kulvik – Ismo Linnosmaa – Joel Shalowitz – Raine Hermans

8.1 Introduction

The previous chapters have dealt with companies' responses to the contradictory government intentions of fostering innovation while seeking to hold down or reduce health care costs. This chapter shows how the interests of the stakeholders can be aligned by presenting a model which explains the links among technology pricing, efficiency of treatment, and long-term health care costs. These dimensions are contrasted with patient utilities received from acute and long-term care.

In evaluating a new technology for approval, the U.S. Food and Drug Administration (FDA) requires evidence of safety and efficacy, but not its economic impact. Further, although the cost-benefit amalyses are common in the health economics literature, the measures they employ do not incorporate long-term social optima based on microeconomic principles. Accordingly, there is need for a theoretical model that can integrate the concepts of the cost structure of the entire health care sector and the non-monetary benefits of social optimization on order to evaluate the true cost-efficiency of new health care technologies. This chapter presents such a model by using clinical examples of two new clinical innovations. In explaining the framework, how implementation of these technologies affects the long-term cost structure as well as measures of patient utility is analyzed. The model can, therefore, serve as a publicly transparent tool for a health care planner as well as a pricing technique for health care providers and suppliers.

Figure 8.1 Drug development and drivers of health care markets



8.1.1 Health care trends

When people buy pharmaceuticals, they do not primarily buy grams or other quantities. They buy pain release, cure, or some other effects. If there are many competitors for the same indications, the consumer purchases quantities of medicines. However, since the patients and physicians prefer the most efficient treatment over any substitute, the price level should be contrasted to the effectiveness of the pharmaceutical and not the unit price with the same logic as in other high technology industries.

The health care sector has reached a major crossroad in many Western countries. In particular, advances in medical science, rising pressures from a growing elderly population, and the discovery of previously unknown disease mechanisms bring with them new and more effective treatments causing rapidly increasing cost pressures.

However, some recent technological applications are expected to spawn cost savings over the long run by, for example, making time-consuming diagnostic methods more efficient and facilitating more timely targeted therapy. Examples of diseases amenable to savings are strokes and schizophrenia, the former being a problem of the elderly population and the latter an illness affecting 1% of the entire world's population. If more efficient ways can be found to make diagnoses and treat patients who would otherwise need long-term treatment, even relatively expensive methods can generate considerable cost savings.

Despite potential long-term advantages, technology approval regulation rarely considers future cost savings. For instance, the US, Food and Drug Administration (FDA) requires evidence on safety and efficacy, but no evaluation of the economic impacts. In other countries, cost-benefit decisions are made based on short-term factors, such as comparative costs of existing competing technologies. There are many reasons for this perspective and their relative importance varies by country. These reasons include culture (such as short-term versus long-term orientation) and economics (the ability to invest in the short term to gain long-term benefits).

Although there are many cost-benefit analyses in the health economics literature, these measures do not usually assess or recommend a balance between costs and benefit to achieve a social optimum between acute intervention and long-term treatment. Therefore, there is a need for a theoretical model, which provides an analytical framework for addressing this issue and arriving at a rational resource allocation recommendation.

This chapter analyzes how the implementation of new technological applications in acute treatment affects the long-term cost structure of health care and relates these measures to patient utility. It is assumed that the patient utility from getting cured in acute treatment is always higher than the patient utility resulting from any long-term treatment or death. This makes it possible to compare the monetary value of cost impacts of a new technology and relate these measures to the patient utility. To this end, the monetary cost impacts of the new technology can be separated and the price for any improvements in patient utility offered.

The model is applied to two rather different real-life cases. The empirical findings suggest two main conclusions. First, regarding a prevalent disease, even small improvements in efficiency of a new technology may result in the price of incremental patient utility to be negative, which implies that the health care payer can reduce total costs and increase the patient utility by adopting the new treatment. Second, regarding a rare disease, the similar outcome will occur only if the patient base is large enough, or the efficiency of the new technology is significantly higher than its conventional substitutes can provide, which signifies that the technology supplier can find a target level for pricing on a given level of treatment efficiency or vice versa. If the treatment efficiency proves to be lower than intended, the project can be cut even at an early stage. This would be the only way to act profitably as a part of a global value network.

A supplier has at every stage of a development process to consider the end-markets, that is, the needs of all distinctive stakeholders. The stakeholder-oriented view signifies that a product or service must add customer (stakeholder) value. Such strategic planning of marketing is already essential at the very initial development stages, and one should even consider how the customer's customer, or stakeholders

even further downstream, can create value with an application. The model can act as a tool for a health care planner as well as a pricing basis for a health care provider, with transparency being the embedded denominator.

8.1.2 Analytical background

Quality-Adjusted Life-Years (QALY) has in recent years become the most commonly used method in economic evaluation in the health care field (Blomqvist, 2002; Dranove, 2003; Baker et al., 2005; Dolan et al., 2005). It has been recommended by the National Institute for Clinical Excellence (NICE) in UK for use in cost-utility analyses of health technologies, and even compared to basic Cost Benefit Analysis (Bateman et al., 2003; Dolan et al., 2005; Phelps and Mushlin, 1991; Johannesson, 1995; Garber and Phelps, 1997; Bleichrodt and Quiggin, 1999 and Dolan and Edlin, 2002).

The concept of QALY itself has been discussed critically on several aspects, but the greatest concerns have been around the assumption of linearity of the model and the correctness of the social dimensions of QALY. QALY is sensitive to the method used, such as time trade-off versus standard gamble, as well as the study setups (e.g. Cook et al., 2001; Richardson et al., 1996; Bleichrodt and Johannesson, 1997; Treadwell, 1998; Treadwell et al., 2000; Bala et al., 1999; Unic et al., 1998; Sackett and Torrance, 1978; McNeil et al., 1981; Miyamoto and Eraker, 1988; Stalmeier et al., 1997; Johannesson and Johansson, 1997). Moreover, QALY has been claimed to introduce values to the monetary calculations in a manner that does not show robustness or which might not reflect the social preferences adequately (see, e.g. Blomqvist, 2002; Harris, 1991; Dolan, 1998; Nord, 1993; Ubel et al., 1999; Cookson and Dolan, 1999; Ubel et al., 1999; Hadorn, 1991; Shmueli, 1999; Anand and Wailoo, 2000; Choudhry et al., 1997; Olsen 2000; Rodriguez-Miguez and Pinto-Prades, 2002; Ubel et al., 2001). For a further discussion, see Dolan et al., 2005 and Blomqvist, 2002, with references therein.

Willingness to pay (WTP) has in recent years been used in conjunction with QALY in assessing net benefit of medical interventions (Remak et al., 2005; Borgstrom et al., 2006; Deutsch et al., 2006; Rubenstein and Inadomi, 2006; Berg et al., 2007; Fox et al., 2007; Hurley et al., 2007; Lyman et al., 2007; Rutten-van Molken et al., 2007; Steuten et al., 2007; Thompson Coon et al., 2007; Quigley et al., 2008). However, critical concerns have been raised both concerning the validity of Willingness to pay (WTP) for a QALY, and the use of QALY as such. Empirical estimates of WTP for QALY have yielded results ranging from 0.20 NOK (€ 0.03) to US$ 49 133 (€ 31 186) per QALY (Cunningham and Hunt, 2000; Blumenschein

and Johannesson, 1998; Zethraeus, 1998; Bala et al., 1998; Olsen and Donaldson, 1998). Such a large diversity understandably casts doubt on the validity of using WTP for QALY. For further discussions on using WTP for QALY, see Blomqvist, 2002 and Baker et al., 2005, with references therein.

8.1.3 Overview of the modeling

This article investigates how the implementation of new technological applications in acute treatment affects the long-term cost structure of health care. To this end, a formal theoretical apparatus is first constructed in which a new technology can be applied in acute intervention. This application, in turn, affects the number of patients requiring long-term treatment. The aim of the theoretical model is to show how the patient utility and monetary costs obtained from the adoption of new technology in acute intervention can be related to those for long-term treatment. For this article, long-term treatment is defined as the need for chronic use of medical products (such as pharmaceuticals and devices), medical services, as well as required social services (such as home or institutional care).

Following the discussion by Buxton et al., 1997, the aim is to construct a model that will:

1. be kept as simple as possible,
2. be as transparent as possible,
3. be possible to generalize to several setups,
4. offer an adequate comparison with current care(s),
5. respect the quality of the data in the model, especially keeping the hard and soft data separated,
6. allow assessing robustness with appropriate sensitivity testing.

Finally, the model will be tested with empirical cases, preferably with highly different characters.

The first empirical case measures the monetary impacts of the introduction of a new technology for the treatment of strokes, the major cause of somatic disability and the second leading cause of death, with a global burden of 6 million ischemic strokes per year and an estimated 4.4 million individuals dying annually as a result thereof. The second case concerns a relatively rare disease, glioblastoma multiforme, affecting approximately 9,000 patients annually. Glioblastomas are the most severe primary brain cancer type: less than 3% of the patients are alive 5 years after diagnosis. In other words, the first illness has huge impacts on overall health care costs, whereas the second case deals with severe disease with lesser effects at the macro level.

The remainder of this article is organized as follows. First it analyzes the choice of a technology in acute intervention. The choice depends on the prices and effectiveness of technologies. As an end point of theoretical setting, the model presents the social optimum for a basis of empirical analysis. Section 2 measures the monetary impacts of adoption of new technology and relates these figures to the marginal utility of a recovering patient in the two empirical cases. These cases represent concrete examples on how the health care payer can utilize the model as a tool for reconciling the non-monetary benefits with the cost-efficiency of the technology adoption. Appendix 8 presents the theoretical model.

8.2 Empirical cases

The model is tested on two real-life cases chosen from diseases treated at the Helsinki University Central Hospital. The first case represents the introduction of a new technology for the treatment of ischemic stroke, the major cause of somatic disability and the second leading cause of death, with a global annual incidence of 6 million cases causing an estimated 4.4 million deaths. (Murray and Lopez, 1997; Wardlaw et al., 2003).

The second case concerns a relatively rare disease, *glioblastoma multiforme*, affecting approximately 9,000 patients annually. However, glioblastomas are the most severe primary brain cancer type in humans: less than 3% of the patients are alive at 5 years after diagnosis (Ohgaki and Kleihues, 2005). Thus, there is an urgent need for more efficient therapy.

The acute intervention and long-term treatment in both cases are provided by Helsinki University Central Hospital (HUCH) and the regional hospitals, all serving under the Hospital District of Helsinki and Uusimaa (HUS).

8.2.1 Construction of an empirical model

The formal model presented in appendix 8 yields a two-part proposition, one for the case where the relative price increase of a new technology equals or is higher than the relative increase in effectiveness, and the other for an opposite situation. The outcome of this proposition can be modified as $V(q) = v(q) - c(q)$. Thus, the inequalities can be rewritten as follows:

if $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$, then technology 2 is socially optimal when

(8.1a) $$u_l - v(q) \geq \frac{p_2 - p_1}{n(\tau_2 - \tau_1)} - c(q) \ ,$$

technology 1 is optimal if

(8.1b) $$\frac{p_2 - p_1}{n(\tau_2 - \tau_1)} > u_l - v(q) \geq \frac{p_2}{n\tau_2} - c(q) \ ,$$

and the minimum care technology is socially optimal whenever

(8.1c) $$\frac{p_1}{\tau_1 n} - c(q) \geq n\left[u_l - v(q)\right] .$$

Similarly, if $\frac{\tau_2}{\tau_1} \geq \frac{p_2}{p_1} > 1$, technology 2 is socially optimal whenever

(8.2) $$u_l - v(q) \geq \frac{p_2}{\tau_2 n} - c(q)$$

and the minimum care technology 0 is socially optimal otherwise.

The criteria above guide to a social optimum by distinguishing the prices and benefits of the technologies implemented at acute intervention and the intensity of long-term care, respectively. This choice is discussed in detail in the last section, Conclusions and Discussion.

8.2.2 Stroke

Stroke is the most common type of cerebrovascular disease. It requires several days of acute treatment frequently followed by a long rehabilitation period, which has led to an increase in treatment costs. Patients suffering from stroke require an average of about 2.5 years of treatment, which in the Helsinki region corresponds to a cost of approximately 100,000 € per patient (Kaste et al., 1998; City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c).

The Department of Neurology at the Helsinki University Central Hospital (HUCH) offers stroke patients ultra-acute thrombolysis, in which the critical blood clot is acutely dissolved. Thrombolysis is part of an efficient and costly treatment chain consisting of prompt patient screening, computer-aided neuro-imaging and diagnostics, thrombolytic therapy, and continued treatment in a specialized stroke unit. In order to be effective, the thrombolysis must be initiated within 4.5 hours

after the first signs of a stroke (Hacke et al., 2008). Alteplase, a glycoprotein produced utilizing recombinant DNA technology, serves as the thrombolytic agent, and the costs of the product alone exceed 1,000 euro per dose.

In the model, the acute intervention unit is represented by the Neuro-Emergency Unit (NEU) at HUCH, and the long-term treatment provider by the supporting hospitals to which HUCH refers the patient no longer in need of acute and most advanced treatment.

Technology 0 represents a situation where the patient is directly admitted to a supporting hospital, that is, no specific treatment is available. This situation is still a reality for patients such as elderly disabled people, who are directed primarily to the supporting hospitals. No further intensive interventions are implemented, and thus the patients do not incur costs for the acute intervention (representing low and high technology, technology 1 and 2, respectively); all costs are carried by the supporting hospitals.

Technology 1 consists of prompt diagnosis, specialized supportive acute treatment and early onset of intensive rehabilitation, all performed at HUCH and generating cost. The specialized supportive treatment consists of 24-hour surveillance, active monitoring and treatment of heart rate, blood sugar and blood pressure, pain, nausea, consciousness, and any new signs and symptoms of deterioration. Due to a more efficient treatment at the acute phase, the survival of stroke patients is higher and thus the patient stream to hospitals providing long-term treatment might increase (Audebert et al., 2008). However, the patients usually require less assistance owing to the payoffs of early rehabilitation and a shorter total treatment time, leading to lower total costs for the sub-acute and long-term treatment (Audebert et al., 2008).

Technology 2 introduction has required additional investments by HUCH, in order to implement a new treatment system. The strict 4.5 hour time window requires:

1. Short response times to emergency calls from patients
2. Efficient on-site diagnosis capability
3. Sophisticated imaging techniques and advanced laboratory services available within minutes from the arrival of patient
4. Specially trained and certified staff for performing thrombolysis
5. Resources available for high-intensive monitoring of patients that have received the therapy.

Variable costs include expenses incurred from running the functions above, but particularly from the use of the thrombolytic drug.

With the introduction of thrombolytic therapy at NEU, the neurological wards at HUCH and the long-term treatment providers have benefited from significant

savings due to a diminished stream of severely ill patients. This benefit is derived from those patients who are virtually cured at an early stage and need less subsequent support and rehabilitation interventions. In 2002, about 8% of the stroke patients coming to the HUCH neurological clinic received thrombolysis; by the end of 2003 the number had doubled. The time window for thrombolysis was extended from 3 to 4.5 hours at end of year 2008. As data is not yet available from the effects of the extended time period, our calculations are based on data from the earlier period with a 3 hour time window. The new extended time window will in future probably show as a further increased number of stroke patients receiving thromboysis.

About 60% of the patients receiving thrombolysis fully recovered. The total cost savings with respect to the recovered patients have been estimated to be approximately 84,000 € per patient (Kaste et al., 1998; Lindsberg et al., 2000; City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c) the savings represent over 80% of the non-recovering patients' total treatment costs (Lindsberg et al., 2000). Most of the savings comes from the costs after the first year (Kaste et al., 1998), where health care personnel expenses constitute the most significant share of the costs.

Defining the parameters for ischemic stroke

The **regulator** is the Hospital District of Helsinki and Uusimaa, HUS.

The **acute intervention** is represented by the Department of Neurology at HUCH and regional hospitals, all serving under HUS. As significant recovery can be seen especially during the first post-stroke year, the acute phase is here defined to include direct costs incurring from intensive treatment up to one year after the initial stroke incident.

The **long-term treatment** is provided by the regional hospitals of Helsinki and Uusimaa, all serving under HUS. The bulk of costs from long-term treatment incur after the first year from the initial stroke incident (Kaste et al., 1998; Lindsberg et al., 2000).

The **number of patients** is 2,000 per annum (Lindsberg et al., 2000).

Technology 0, $\mathbf{t_0}$, consists of supportive care given at the regional hospitals. This care is a baseline treatment and does not incur additional costs; thus **p0** = 0.

Technology 1, $\mathbf{t_1}$, is offered initially by the Stroke unit at HUCH and continued up to 1 year after the stroke incident. It includes specialized acute-phase care after a stroke, as well as intensive rehabilitation both in HUCH and in the regional hospitals. The price increase when introducing technology 1 is derived from the diagnosis-related group (DRG) price for treating one uncomplicated stroke at the

teaching university hospital[1]; $\mathbf{p_1}$ = 8.12 M€ (HUS, 2005b).[2] The DRG price includes both intensified acute treatment as well as basic care; however, as an intensified acute treatment leads to a higher survival rate and thus increases total treatment given, it is assumed that the DRG price reflects sufficiently well the true total additional costs induced by technology 1.

Technology 2, $\mathbf{t_2}$, is employed over a series of events, beginning at the site of the stroke and ending either after a decision not to give thrombolytic therapy, or at the Stroke Unit after thrombolysis. The additional costs induced by the addition of thrombolytic therapy are offset by the savings resulting from reduced disability during the first year (Fagan et al., 1998). Thus, the short-term price for treating one stroke with Alteplase (technology 2) is: p2 = 8.12 M€ (HUS, 2005).[3]

Severity of illness at referral to the acute intervention provider is defined as severe ischemic stroke yielding three or more points on the The National Institute of Health Stroke Scale (NIHSS).

The health care budget B is set by a regional political council with representatives from all communities in Helsinki and Uusimaa that refer patients to HUS. The total budget for stroke treatment in the Helsinki and Uusimaa region is approximated to be 80 million euro annually (Kaste et al., 1998; Lindsberg et al., 2000; City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c).

The share of budget allocation to acute intervention μ is set by HUS. Typically, the acute and long-term sectors have separate budgets. HUS was established in order to facilitate coordinated budget allocation between acute interventions and long-term treatment. In this example, the initial costs of introducing technologies 1 and 2 were fully born by the acute intervention provider, but without a change in the budget allocation μ.

The obtained **utility** $\mathbf{u(a^h)}$ and $\mathbf{u(a^l)}$ are defined as the end-points of **high** and **low severity of disease after acute treatment**, respectively. In this paper, the modified Rankin scale is used as a criteria for independence: a score of 0 – 2 is approximately equivalent to independence, and it corresponds to a score of > 18 on the Barthel Index (Wade, 1995). Consequently, a modified Rankin score of 0

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[1] The 2005 DRG price was used to reflect the treatment costs since: 1) the 2005 DRG-price did not yet include the price of thrombolytic therapy, 2) patients that received therapy by technology 0 were treated outside HUCH and hence did not influence the DRG-price, and 3) virtually all patients entering HUCH received therapy with technology 1 (but not 0 or 2).

[2] $\mathbf{p_1}$ = 4,060 € / patient * 2,000 patients = 8.12 M€.

[3] p2 = (4,060 € / patient * 1,900 patients) + (4,060 € / patient * 100 patients) = 8.12 M€.

– 2 demonstrates low severity of disease, and high severity is defined as a score of > 2. The obtained utility is evaluated at one year after the stroke as a function of the end-point and the probability of achieving that end-point.

For the **acute intervention phase** the utility from treatment is defined to be zero, $u_1 = 0$, when the Rankin score remains > 2; and with a score of 0 – 2 the patient experiences a positive utility from the treatment, and $u_1 > 0$.

The **probability of having a low severity of disease**, that is, having a modified Rankin of 0 to 2 after receiving treatment at the acute intervention is 0 for the reference technology 0 ($\tau_0 = 0$), 0.22 for technology 1 ($\tau_1 = 0.220$) and 0.227 for technology 2 ($\tau_2 = 0.227$) (Wardlaw et al., 2003; Cochrane, 2007).[4]

Slackness S is usually perceived as an unwanted way of allocating resources, and thus S is preferably minimized. The assumption holds also with all units in HUS.

The **number of stroke patients** is 2.000 annually; n=2000.

Two parallel methods for counting **the average cost c(q)** of treating one Finnish stroke patient with basic technology (p_0) are utilized. The costs have originally been calculated with an extrapolation to 1991 (Kaste et al., 1998). In the first calculation the same assumptions as in Kaste et al. (1998) are used, that is, a discount rate of 5% and an increase of productivity by 1.5%. This calculation yielded an average cost of 86,548 euro per patient for 2004. In the r second calculation the unitary costs of health care and social services needed in the treatment of stroke patients that were used as a basis for the calculations in 1987 were related to the corresponding costs in 2004 (Kaste et al., 1998; City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c). The second calculation yielded a cost of 75,682 euro per patient. The average of these two calculations yields as c(q) 81,115 euro per stroke patient treated with technology zero.

8.2.3 Boron neutron capture therapy

Glioblastoma multiforme has eluded efficient therapy, with the most efficient available treatment offering roughly a doubling of the median survival time to approximately 40 weeks after diagnosis (Andersen, 1978; Walker et al., 1978; Walker et al., 1980; Chin et al., 1981; Kristiansen et al., 1981). In an attempt to offer significant improvement to the prognosis of this deleterious disease, the Finnish Boron

[4] Proportion of eligible patients for thrombolytic therapy x risk reduction = 0.22+[0.05 x 0.14] = 0.227.

Neutron Capture Therapy (BNCT) project was launched in 1994. In this paper it is defined as **technology 2**.

BNCT is based on boron-10 atoms coupled to a carrier molecule with an affinity towards malignant cells. Once inside the cancer cell, the boron-10 molecule (^{10}B) is activated by neutrons and disintegrates quickly giving rise to closely spaced ionizing events with a high linear energy transfer (LET). The high LET irradiation induces injuries with little if any cellular repair, but only near to, on, or within the cells containing ^{10}B atoms. Thus, the tumor cells are eliminated but the normal tissue is spared.

In basic treatment **(technology 0)** the patient is diagnosed and given supportive care, which includes neurosurgical removal of the visible tumor mass. In some cases the patient can be severely ill at time of diagnosis or the location of the tumor can inaccessible, contraindicating normal treatment measures; these patients are, however, exceptions.

A patient not presenting with specific contraindications is usually offered concomitant radiation after the neurosurgical debulkment. **Technology 1** is defined as consisting of 1. a neurosurgical operation with the aim of removing all malignant tissue, and 2. a full series of radiation therapy sessions, in addition to normal supportive procedures and therapy.

Technology 2 encompasses 1. a normal neurosurgical operation, followed by 2. BNCT-treatment as described above. The introduction of technology 2 has required major investments: extensive modifications of the nuclear research reactor FiR-1 in Espoo (Auterinen et al., 1998), quality assurance measures thereof (Auterinen et al., 2004; Uusi-Simola et al., 2004), development of a boron measurement system (Laakso et al., 2001), preclinical safety testing (Kulvik et al., 2004). and the complete development work from synthesis experimentation to clinical applications for the boron-carrier-complex (Kulvik et al., 2003).

The patient treatments started in 1999 through a specific BNCT treatment company, and the treatments have been ongoing ever since (Joensuu et al., 2003; Kankaanranta, 2005; Pakkala, 2005).

Defining the parameters for glioblastoma treatments

The main treatment is always given in a University hospital, where the treatment costs are intercomparable. Additionally, because BNCT is performed only in HUCH, the interventions provided there are used as representing the whole country.

For the model the following parameters can be defined:

- The **regulator** is the Hospital District of Helsinki and Uusimaa, HUS. However, there will still be only one BNCT treatment station in the fore-

seeable future, and as *glioblastomas* are rare, the implementation will cover all of Finland.

- The **acute intervention** is provided by the Departments of Neurology, Neurosurgery and Oncology at HUCH, serving under HUS. The acute phase is here defined to include direct costs that are additional to normal treatment costs for patients suffering from *glioblastoma multiforme*.
- The **long-term treatment** is provided by HUCH and the regional hospitals of Helsinki and Uusimaa, all serving under HUS. As opposed to stroke, the bulk of long-term treatment is delivered during the first year following diagnosis.
- The **number of patients** is approximately 150 per annum (Ohgaki and Kleihues, 2005).

Technology 0, $\mathbf{t_0}$, consists of prompt diagnosis, acute intervention, a neurosurgical operation. and supportive care given initially at HUCH and later mainly at the regional hospitals. This is a baseline treatment and does not incur additional costs; thus $\mathbf{p_0} = 0$.

Technology 1, $\mathbf{t_1}$, is offered by the Department of neurology at HUCH (diagnosis and acute intervention), the Department of Neurosurgery at HUCH (neurosurgical debulkment and histological-pathological diagnosis of tumour), and the Department of oncology at HUCH (radiation therapy); of these, however, only the radiation therapy incurs additional cost when compared to technology 0. As the equipment is used mainly for the treatment of other, more frequently occurring, diseases, accrue initial fixed costs for the introduction of technology 1 are not accrued; the fixed costs are adequately included in the DRG price for *glioblastoma multiforme*. The price increase when introducing technology 1 is derived from the diagnosis-related group (DRG) price for treating one *glioblastoma multiforme* -patient at HUCH; $\mathbf{p_1}$ = 2,420 euro / patient * 150 patients = 363,000 euro (Neurology, 2005; Neurosurgery, 2005; Oncology knowledge center Hospital District of Helsinki and Uusimaa, HUS 2005; HUS, 2005a). As an intensified acute treatment leads to a longer survival time, it is assumed that the DRG price adequately reflects the true total additional costs induced by technology 1.

Technology 2, $\mathbf{t_2}$, consists of a series of events and interventions, starting with those of technology 1. The additional costs induced by technology 2 consist of allocated fixed and variable costs associated with BNCT therapy, less the price for giving a full series of conventional radiotherapy (which BNCT replaces). As several other brain cancer treatment modalities are under continuous research, and especially as accelerator based neutron sources are under intensive development, it is assumed that the effective life cycle for nuclear reactor based BNCT is 10 years, after which the technology has become too obsolete to be competitive (Blue and Yanch, 2003;

Svensson and Moller, 2003; Kononov et al., 2004; Lee et al., 2004). The first patient in Finland was treated on May 1999, and by May 2005 42 brain tumour patients received BNC-treatment (Kankaanranta, 2005). Projecting a steadily rising patient stream, it is somewhat optimistically assumed that 100 more patients will be treated in the next four years. It is additionally assumed that the increasing patient stream brings about savings due to a streamlining of the procedures, which compensates for the impact of inflation on costs. Keeping the price for one treatment at the 2005 level, that is, 20,000 euro, a price for technology 2 is obtained: $\mathbf{p_2}$ = 890,120 euro.[5]

Severity of illness at referral to the acute intervention provider is defined as glioblastoma with clear symptoms of disease and a Karnofsky score below 70; the Karnofsky score will be discussed in more detail below.

The health care budget B is in principle set regionally by respective political councils or their equivalent. However, in the case of rare diseases with interventions centralized to university hospitals, the budget is set by the respective university hospitals. As BNCT is given solely at HUCH, the decisions are made by a political council with representatives from all communities in Helsinki and Uusimaa that refer patients to HUS. The total budget for treatment of glioblastoma multiforme in Finland to be 4,440 million euro annually (Neurological department Hospital District of Helsinki and Uusimaa HUS, 2005; Neurology, 2005; Neurosurgery, 2005; Neurosurgical department Hospital District of Helsinki and Uusimaa HUS, 2005; Oncology knowledge center Hospital District of Helsinki and Uusimaa HUS, 2005; City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c)[6].

The share of budget allocation to acute intervention μ is also in brain tumor treatment set by HUS. However, in contrast to treatment of stroke, only the initial costs of introducing technology 1 were born by the acute intervention. The establishment of the BNCT treatment station was strongly supported by the National Technology Agency of Finland and therefore HUCH incurred no additional costs. Te model intends, however, to take as broad a view as possible, and thus the fixed costs for technology 2 are also included in the calculations. As the funding is external, μ is not changed.

The obtained **utility** $\mathbf{u(a^h)}$ and $\mathbf{u(a^l)}$ are defined as the end-points of **high** and **low severity of disease**, respectively. The Karnofsky Performance Scale combines

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[5] Price for technology 2 p2 = (2,420 € / patient * 136 patients / year) + 2,000,000 € / 10 years + 20,000 € / patient * 14.2 patients / year = 329,120 + 200,000 + 280,000 € = 890,120 €.

[6] This consists of initial treatment costs of (2,400 € + 7,020 € + 2,420 €) = 11,840 / patient (diagnosis, initial treatment, neurosurgery and radiation therapy) and a three month late stage period totalling 16,200 €, where the patient is again in need of intensified support and treatment.

the degree of disease with a person's ability to care for themselves (Karnofsky, Abelmann et al., 1948). While it is widely used, it offers only a rather arbitrary assessment of severity of disease (Slevin et al., 1988; Murray et al., 1995; Green, 1997). However, since it has been commonly used in clinical trials concerning brain tumor treatment, it is used for the purpose of this study. Consequently, a Karnofsky score of ≥ 70 (70 = Cares for themselves, unable to perform normal activity or to do active work) is defined as demonstrating low severity of disease, and high severity is defined as a Karnofsky score of < 70.

The obtained utility is evaluated at one year after diagnosis as a function of the end-point and the probability τ_t = of achieving that end-point.

At the end of the **acute intervention phase** if a patient has a Karnofsky score of ≥ 70 this is defined as having experienced a positive utility from the treatment $u(a^l) > 0$, -even if the patient started with a score > 70, the treatment can prevent deterioration. On the other hand, if the Karnofsky remains below 70, the utility: $u(a^h) = 0$.

Slackness S is usually perceived as an unwanted way of allocating resources, and thus S is preferably minimized. The assumption holds also with all units in HUS.

150 **patients** are diagnosed annually with *glioblastoma multiforme*.

The enhanced **probability of having a low severity of disease** after basic treatment, that is, a Karnofsky score of ≥ 70 at one year after diagnosis, is 0 for technology 0 ($\tau_0 = 0$), 0.082 for technology 1 ($\tau_1 = 0.082$) (Kristiansen et al., 1981; Laperriere et al., 2002)[7]. For BNCT, the developers strived for an enhancement of τ by 50%[8], yielding $\tau_2 = 0.123$ (Kallio et al., 1997).

The average cost c(q) of treating one Finnish glioblastoma patient with reference technology 0(p_0) is derived by combining several data sources. The DRG price 2,400 euro/patient reflects costs accrued from initial diagnosis and treatment (Neurological department Hospital District of Helsinki and Uusimaa HUS, 2005). The initial CT-scan has to be complemented by an MR-imaging and followed by neurosurgery, adding up to a total cost of 7,020 euro (Neurosurgical department Hospital District of Helsinki and Uusimaa HUS, 2005). Costs related to radiation therapy are excluded. With such treatment the weighted average median survival

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[7] τ_1 was derived by combining 1. Performance data on glioblastoma patients after operation and radiotherapy with or without chemotherapy, yielding an average 62% of patients not capable of caring for self at one year, with 2. Risk ratio for 1-year mortality of post-operative radiotherapy versus no radiotherapy = 0.81; these correspond to the terms σ_t and δ_t in equation (2), respectively.

[8] The enhancement reflected anticipations of both a better survival for a subpopulation as well as a better quality of life as assessed by ability of caring for self.

of patients is 18 weeks, with an initial improvement phase, a long phase of deterioration, and concomitantly an increasing need of care with occasional visits to an acute intervention unit (Chin et al., 1981; Laperriere et al., 2002). The supportive phase is about two thirds of the total survival time (Kristiansen et al., 1981), and thus the average price of later stage treatment is approximated to 17,762 euro (City of Helsinki, 2005a; City of Helsinki, 2005b; City of Helsinki, 2005c).[9] The reference technology yields a total average cost of 27,182 euro/patient.

8.3 Results

The derived values for stroke and *glioblastoma multiforme*, respectively are collected below (Tables 8.1 and 8.2).

Stroke

By entering these values into proposition 1, it can be seen that the three zero-slack allocations (s=0) result in the values {**0, 0.1015, 0.1015**}, indicating that for optimal treatment intensity, μ should get a value of 0 or 0.1015. As technology 2 incurs no additional costs compared to technology 1, the health care payer is initially indifferent between technologies 1 and 2.

Proposition 2 makes a distinction between whether $\frac{p_2}{p_1}$ is smaller than $\frac{\tau_2}{\tau_1}$ or not.

As $\frac{\tau_2}{\tau_1} = 1.032$ and $\frac{p_2}{p_1} = 1.00$ and hence $\frac{\tau_2}{\tau_1} > \frac{p_2}{p_1}$, technology 2 according to equation 19. Thus

$$u_l - v(q^*) \geq \text{ - 63,230 € / patient} \qquad (8.3)$$

The inequalities indicate that technology 2 should be chosen if the added value of a successful acute treatment as compared to optimal long-term treatment is appreciated to be an equivalent of -63,230 euro or more. The negative number

[9] The average treatment duration is 83 days and the daily cost 214 €.

Table 8.1 The parameters for stroke

Stroke				
Health care budget	B	80 mill.		
Technology	t	t_0	t_1	t_2
Patients	N	2,000	2,000	2,000
Price of technology	p	0	8,120,000	8,120,000
probability of having a low severity of disease	τ	0	0.220	0.227
Average cost of treatment c(q)	c(q)	81,115		
Results				
Zero slack values	s = 0	0	0.1015	0.1015
Severity of illness	*d*	*l* (low)	*h* (high)	
Obtained utility	v(q)	$u(a^l) > 0$	$u(a^h) = 0$	
corresponding to Rankin	*d*	0 - 2	> 2	
Threshold for adopting new technology	$u_l - v(q^*) \geq$ **-63,230**			

Table 8.2 The parameters for glioblastoma multiforme

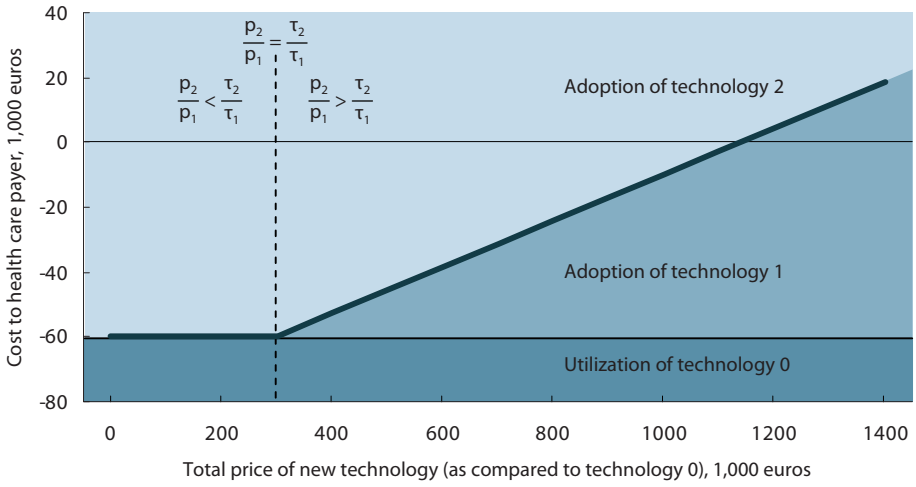
Glioblastoma Multiforme				
Health care budget	B	4.4 mill.		
Technology	t	t_0	t_1	t_2
Patients	N	150	1,501	50
Price of technology	p	0	363,000	890,120
probability of having a low severity of disease	τ	0	0.082	0.123
Average cost of treatment	c(q)	27,182		
Results				
Zero slack values	s=0	0	0.082	0.2
Severity of illness	*d*	*l* (low)	*h* (high)	
Obtained utility	v(q)	$u(a^l) > 0$	$u(a^h) = 0$	
corresponding to Karnofsky	≥ 70	< 70		
Threshold for adopting new technology	$u_l - v(q^*) \geq$ **58,528**			

denotes that technology 2 offers a direct economic advantage, and thus the choice between technologies seems evident. A graphical display of the analysis shows that the cost-efficiency frontier for technology 2 breaks the zero level if technology 2 required infrastructure investments of 1.2 million euro as an actual cash outflow in 2005 prices (Figure 8.2); with higher initial investments the treatement would induce an extra cost for each additional recovered patient.

In strict monetary terms, the results reflect the marginal/incremental utility of a successful acute treatment compared to optimal long-term treatment, and 63,230 euro is the monetary value above which the incremental utility should remain in order for thrombolysis to be adopted. This finding is in concordance with the results obtained from traditional economic analyses: treatment of stroke with recombinant DNA based alteplase not only saves lives, but also incurs significant monetary savings for society.

It should be noted, that all other things being equal, $u - v$ should logically be ≥ 0, because long-term treatment can never be preferable to acute intervention if their effect is equal; it would not be meaningful to keep the patient sick for a longer instead of a shorter time. Theoretically, a social dictator might purposely choose

Figure 8.2 The cost-efficiency frontiers in acute intervention treatment of stroke in increasing prices of thrombolytic therapy

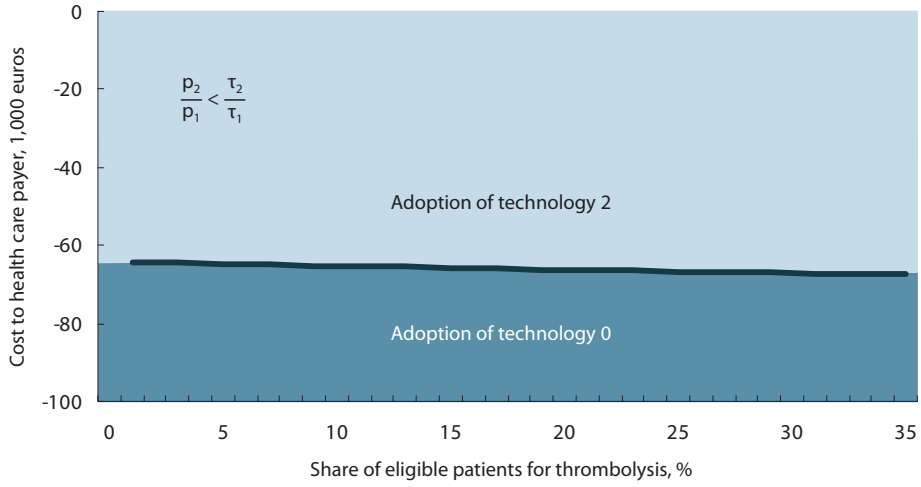


to promote long-term care, even at an additional cost, for example, in order to promote jobs in the sector. In this case, the dictator might choose to spend 63,230 euro/patient so that the hospital can be kept running.

The share of eligible patients for thrombolysis has been a central point in economic calculations concerning this therapy (Hankey and Warlow, 1999; Lindsberg et al., 2000). The model suggests that available data strongly support the rationale for adopting technology 2 irrespective of even significant changes in the achieved eligibility percentages: for eligibility percentages between 1 and 33%, technology 2 remains dominant, with only a marginal change in the achieved utility (Figure 8.3).

Finally, technology 2 remains economically competitive up to a direct additional treatment cost of 15,416 euro, after which the same situation applies as with technology 1: other explanations defend a choice of technology 2 as compared to technologies 1 and 0, but always induce an economic burden for the health care payer.

Figure 8.3 The cost-efficiency frontiers in acute intervention: treatment of stroke with an increasing number of eligible patients for thrombolytic therapy



Glioblastoma multiforme

Proposition 1 yields three zero-slack allocations (s=0) with corresponding values of {**0, 0.082, 0.200**}, indicating that for an optimal treatment intensity μ should get a value of 0.082 or 0.200. Proposition 2 makes a distinction between whether $\frac{p_2}{p_1}$ is smaller than $\frac{\tau_2}{\tau_1}$ or not. As

$$\frac{p_2}{p_1} = 2.452 \text{ and } \frac{\tau_2}{\tau_1} = 1.500 \text{ and hence } \frac{p_2}{p_1} > \frac{\tau_2}{\tau_1} \tag{8.4}$$

technology 2 should be optimal if

$$n[u(a^l) - V(q)] \geq \frac{p_2 - p_1}{\tau_2 - \tau_1}. \tag{8.5}$$

The right side of the inequality can be regarded as emphasizing the economic rationale of introducing a new technology, whereas the left side highlights other, non-monetary arguments in favor of an intensified acute phase treatment.

By plugging in the numbers yielding

$$n[u(a^l) - V(q)] \geq \text{ 85,710€} \tag{8.6}$$

or

$$\Leftrightarrow u(a^l) - (v(q^*) \geq \text{ 58,528€/patient} \tag{8.7}$$

it can be seen that technology 2 should be chosen if the added value (or opportunity cost) of a successful acute treatment compared to optimal long-term treatment is appreciated to be an equivalent of 58,528 euro or more. In other words, technology 2 does not offer any direct economic advantage, and thus the choice between technologies is ambiguous.

This situation is graphically displayed in Figure 8.4, where the cost-efficiency frontier for technology 2 does not break the zero level. High sunk costs (initial investment of 1.2 mill. euro) in development of the technology 2 can be overtaken either by enhancing the patient base and the size of units providing this kind of treatment, or by introducing a new technology with higher direct health effects or

lower cost technology, that is, < 1.2 mill. euro. With the sunk costs that high, the cost-efficiency frontier for technology 2 breaks the zero level with recovery rates no less than 55%, as shown in Figure 8.5.

In the latter case, technology 2 is not economically competitive; however, it can be chosen on other grounds. Such arguments could be: an interest in the technology per se, a vision of a development of the technology to become more competitive, or a lower risk of death or dependency.

The results derived from the utilization of BNCT on glioblastoma-type brain cancers seem in economic terms to be almost opposite to the results of the stroke thrombolysis. The model suggests that the health care payer decides to adopt the BNCT technology as the main application in acute intervention if the payer values a single additional self-caring patient at 58,528 euro.

Figure 8.4 The costs associated with one recovered patient as a function of the probability of achieving good health with technologies 1 and 2

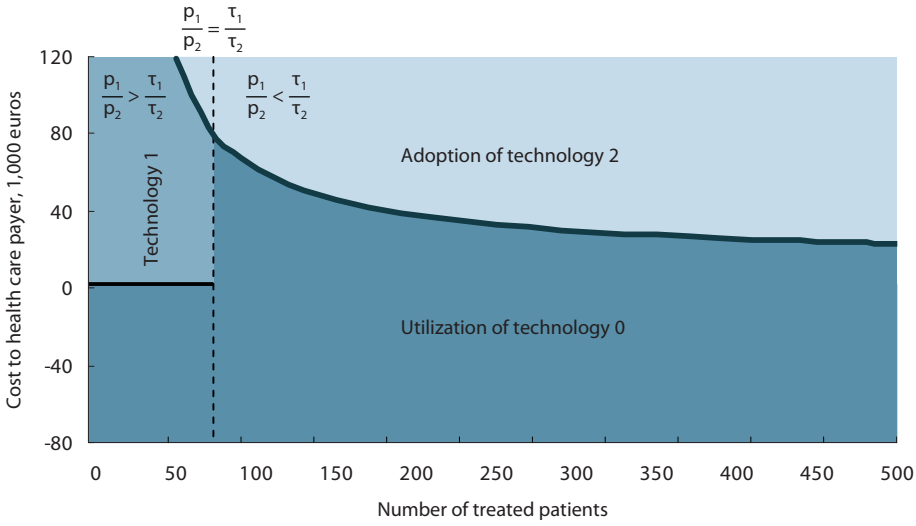
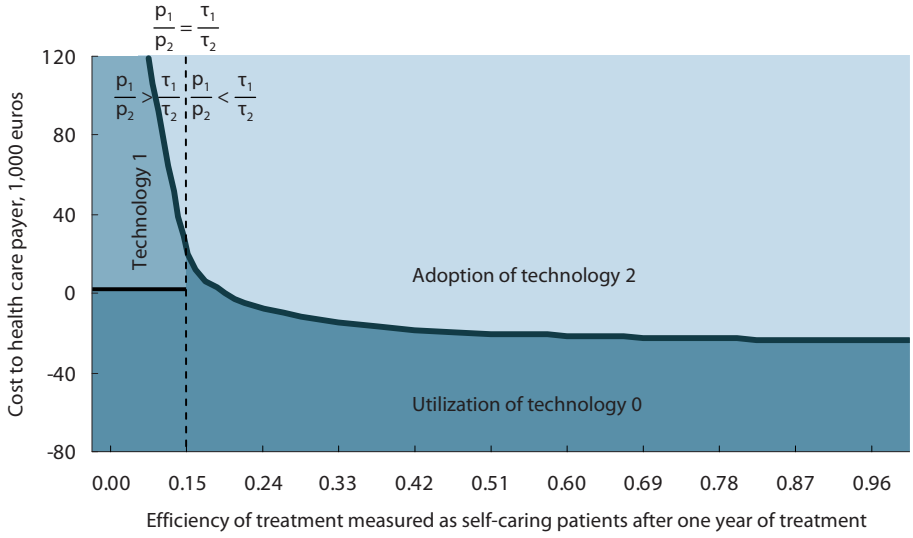


Figure 8.5 The costs associated with the probability of achieving good health with technologies 1 and 2



8.4 Conclusions and Discussion

This study analyses how the implementation of new technological applications in acute treatment affects the long-term cost structure of health care. The non-monetary utility is compared to cost-efficiency impacts of a new technology. A theoretical apparatus is constructed and utilized in two empirical cases: thrombolysis therapy for stroke, and Boron Neutron Capture Therapy (BNCT) on glioblastoma-type brain cancers. The empirical cases indicate how the monetary cost-efficiency of the new technologies can be related to the non-monetary patient utility.

The first empirical case shows, that the introduction of a new treatment technology can induce direct savings for the health care payer. Critical factors are the probability of the treatment being effective, the incidence of the disease, as well as the costs of acute versus long-term treatment and the initial sunk costs. The introduction of the assessed technologies is clearly rational compared to baseline technology.

In the second empirical case, all critical factors are nearly opposite to the first case: it presents a rare disease with a low probability of recovery, high sunk costs

as well as acute treatment costs, but relatively low long-term treatment costs due to the rapidly aggressive progression of the disease. A new technology showing low effect but high initial costs calls for a larger population base. This situation calls for cooperation across national borders.

Finally, four issues will be discussed, which can be dealt with from perspectives different than those above in the model. First, the non-monetary benefits are related to the monetary measures of cost-efficiency of the model. Second, the model provides an assumption on the zero-slackness in acute health care, which is questioned and discussed. Third, some perspectives on the risk profiles and pricing of new technologies especially at the early stage of development are adduced. Fourth, how the probability of the patient dying affects the cost-efficiency calculus will be discussed.

1. Non-monetary benefits vs. monetary cost-efficiency. The benefits from an adoption of new technology can be purely humanitarian, or they might involve economic impacts, typically secondary and indirect, that have not been taken into account in the conventional cost-benefit calculations. Examples of potential benefits are:

- the non-monetary value of avoiding deaths *per se*
- the non-monetary value of an early recovery, leading to a better quality of life
- a preponderance of new technology *per se*
- potential secondary benefits from supporting a novel technology (e.g. applications in other fields or further applications in the same field)
- a preference towards labor intensive solutions.

The above benefits are difficult to measure in monetary terms. The main idea of the presented analysis is, however, that the model enables the comparison between the non-monetary utility and monetary cost-effectiveness. Accordingly, the model presents the non-monetary utility and the cost-effectiveness of acute intervention. The model enables the direct valuation of distinctive policy decisions. For instance, empirical comparison between the BNCT treatment and conventional radiation therapy resulted in the actual improvement in acute intervention efficiency being relatively costly without concomitant benefits after the adoption of BNCT technology. However, the model does not provide strict answers, about whether the payer should adopt of the new technology; instead, it relates the non-monetary benefits to the cost-efficiency of adopting the technology.

Stroke is a disorder plaguing the elderly population in particular and it is important to note that the development of effective and expensive comprehensive treatment applied at the right time has proven to generate significant savings from society's perspective. Therefore, reasoning not to adopt the new technology would be based on a disutility of patient cure.

Introducing a new technology frequently induces additional initial costs. A health care provider who is paid by a global budget has, therefore, an intrinsic barrier to introducing a costly new technology even if that technology is cost-saving in the long run. Additionally, there might be non-intentional factors hampering the introduction of a new technology. Examples of these factors include:

- system inertia (labor unions, sectoral thinking)
- aversion to primary expenditure
- ignorance concerning the positive effects of intensified acute intervention
- reluctance towards new technologies.

2. Organizational Slackness. From an operational point of view, slackness should always be minimized as long as it incurs cost savings. In health care the importance of redundancy (also called excess capacity), is seemingly contradictory to operational efficiency. Redundancy is desirable, however, for public health reasons, such as potential widespread acts of terrorism and threats of SARS or bird flu-type pandemics. If a provider unit is running optimally in an economical sense, according to the above principles, it does not yield a profit or loss. However, such an operating unit can reallocate resources by, for example, shutting down a ward for a certain period, and thus it possesses in reality some discretionary power.

3. Risk profiles and pricing of new technologies. Companies developing health care technologies could use the model in setting their price. Utilisation of simulation techniques and probability distributions would assist the pricing and valuation procedures particularly in the early stage of the development procedures while the variables of the model are unknown or highly sensitive.

4. Probability that the patient dies (for clarity, e the risk of a patient dying will be denoted as δ). The risk of death δ for patients annually referred to the long-term treatment varies with the chosen technology as follows:

Technology 0: all patients access primarily long-term treatment, and thus n_{t0} = 2000. It is noteworthy, that only 62% of these patients will survive their stroke (Numminen et al., 1996). Thus, $\delta_0 = 0.38$.

Technology 1: All patients are primarily treated at a specialized stroke unit, which enhances the survival rate by 11%; consequently, approximately 69% of the patients will survive the initial phase; $\delta_0 = 0.31$ and n_{t1} for the long-term treatment equals 1,377 patients (Cochrane, 2007).

Technology 2: A conservative approach suggests that 5% of all ischemic stroke patients will receive thrombolytic therapy (Lindsberg et al., 2000). Of these, 17% will die (Numminen et al., 1996; Hacke et al., 1998; Lindsberg et al., 2000). However, one out of seven have been reported as regaining independence after severe initial stroke, that is, the number-needed-to-treat (NNT) for avoiding dependence is 7 (Donnan,

1998) (see also Cornu et al., 2001; Donnan and Davis, 2001). In the catchment area of HUS 100 out of 2,000 stroke patients will receive thrombolysis, with 83 patients surviving the treatment and 14 avoiding dependency; without thrombolysis, all 14 would be severely debilitated with a Rankin score above 2. Consequently, $\delta_2 = 0.303$ and $n_{t2} = 1{,}377$ patients will be remitted to long-term treatment.

The technology-dependent risk of death could preferably be included in the model by differentiating between the probabilities of dying or remaining severely ill, respectively. Death can decrease long-term treatment costs, sometimes even with a significant impact, but simultaneously the potential labor input of a patient of working age is lost. The concept of Quality-adjusted life-year (QALY) attempts to address the issue. In doing so, QALY combines non-monetary and monetary utilities (see, *e.g.* Dranove (2003) and citations therein).The intention with the presented model has been to keep the monetary and non-monetary utilities strictly separate [on opposite sides of equation], yet allowing each party to bring their expertise into the assessment process and thereby initiate a solid discussion between the entities involved.

The presented model is built on a theoretically solid microeconomic foundation. The empirical background is from the area of health care, but can also be employed in analyses in other fields when decisions must be made concerning implementation of a new technology.

Appendix 8
Modeling the pricing of the health care innovations

A8 The model

In order to analyze the choices made by health care payers and service providers, the strategic decision-making between the payer and acute intervention and long-term treatment providers is considered. Acute intervention refers to furnishing the initial treatment for patients; long-term treatment refers to treating patients not recovering after receiving acute intervention[10]. These activities can be located in the same or different hospitals. There are n patients in the acute intervention and patients can be treated using one of three treatments, treatment 0, 1, or 2. The set of available technologies is denoted as T = {0, 1,2}. Technology 0 refers to basic care in which all patients receive standard attention and are referred to the long-term treatment provider for further treatment. Since this technology is used as the reference point, it sets a standard cost for the acute intervention: the price of any other technology is compared to this cost. The prices of technologies 1 and 2 for the acute intervention are denoted as p_1 and p_2. It is assumed throughout the text that technology 2 is more expensive but also more effective than technology 1 and $p_1 < p_2$. Prices can measure lump-sum payments which the hospital has to pay for the use of technologies or they can also measure total costs of applying technologies to a certain population of patients.

The severity of disease is denoted as d. Disease categories are divided into two classes, low, l, or high, h, severity. This division is made according to established, measurable criteria. For example, for the diseases discussed below, this distinction is made using the Karnofsky scale with a 70 score as the dividing line. In what follows, a patient is also said to be mildly (that is,, $d = l$) or severely (that is,, $d = h$) ill. It is assumed that all patients entering the acute intervention have a high severity of disease and are in need of treatment. The probability that a patient has low severity of disease after treatment at the acute intervention is given as $\tau_t = Prob(d = l \mid t)$. This probability is conditional on the chosen technology t. All patients that show a high severity of illness after the acute intervention will be referred for long-term treatment. It is assumed that technology 2 is the most effective[11] and the minimum

[10] For more standard definitions of long-term care and treatment, see Norton (2000).

[11] In what follows, effectiveness of a health care technology is defined in terms of probability τ_t

care technology is ineffective in a sense that $0 \leq \tau_0 < \tau_1 < \tau_2 < 1$. This effectiveness ranking means that the application of technology 2 maximizes the number of patients with only mild illness, and technology 1 offers results better than baseline therapy but inferior to technology 2. Although in reality a fraction of patients may die as a result of applying technology 1 or technology 2, it is assumed that this fraction is always sufficiently small to be ignored in the formal analysis.

Patients obtain utility levels u_l and u_h from being treated for their illness.It is assumed that a patient has obtained no utility if the severity of disease at the end-point is still high, that is, $u_h = 0$, and the patient obtains a positive utility level in case the illness is only mild, that is,, $u_l > 0$, after acute intervention. Therefore, a representative patient obtains expected utility $\tau_1 u_l$ at the acute intervention. The aggregate expected utility for patients in the acute intervention is then

$$EU(t) = n \tau_1 u_1. \qquad \text{(A8.1)}$$

It is assumed that both providers operate under a zero-profit constraint (see Newhouse, 1970; Chalkey and Malcolmson, 2000). The objective of the acute intervention is to maximize aggregate expected utility obtained from alternative treatments subject to the constraint that the provider earns zero profit. The zero profit constraint for the acute intervention can be defined as $\mu B - s - p_t = 0$, where μB is the share of expenses paid from health care payers' budget to the provider. This concept is referred to below as *health care budget*. It is assumed that any resources which the provider obtains over and above the price of the chosen technology is spent on organizational slack, measured by the variable *s*. The term slack includes 1) pure technical inefficiency, 2) accumulating reserves, or 3) purposeful slackness (preparedness for unexpected events).

The total cost function of the long-term treatment is $C(q,n) = c(q)n(t)$, where $c(q)$ measures the average cost of treating one patient with treatment intensity $q > 0$ and $n(t)$ is the number of patients treated in the long-term treatment provider. It is assumed throughout this paper that the unit cost function $c(q)$ is a monotonically increasing and continuous function of the long-term treatment intensity q and $c(0) = 0$.

This model creates a connection between treatment decisions at the acute intervention and the demand for and costs of long-term treatment. In particular, the number of patients in the long-term treatment can be defined as $n(t) = (1-\tau_1)n$ and depends on the health care technology chosen by the acute intervention unit. Consequently, the more effective the technology at the acute intervention, the fewer patients will need services in a long-term treatment facility.

The revenue of the long-term treatment unit is determined purely by the health care payers' budgetary decisions[12]. If the payer allocates fraction μ of the budget to the acute intervention, the long-term treatment unit obtains a revenue of *(1 - μ)B*. The payoff of the long-term treatment can be defined as

$$L(q,\mu,t) = (1-\mu)B - n(1-\tau_t)c(q) \qquad \text{(A8.2)}$$

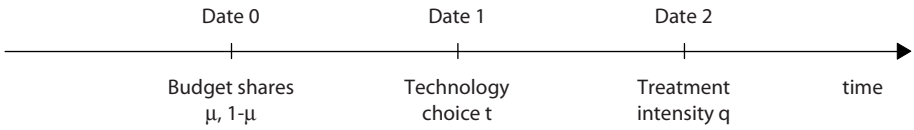
If for a given choice of treatment intensity $L(q,\mu,t) > 0$ the provider retains a profit, and if $L(q,\mu,t) < 0$, the health care payer has to supply the long-term treatment with more resources. However, as μ and B are chosen by the health care regulator, and the probability of recovery is a function of technology choice made by the acute intervention, the long-term treatment provider can conform to the requirement of zero profits and adopt a treatment intensity q for which $L(q,\mu,t) = 0$.

It is assumed that each patient obtains a (monetary-equivalent) benefit $v(q)$ from treatment intensity q at the long-term treatment. It is also assumed that $v(0) = 0$ and that the benefit function $v(q)$ is increasing and continuous with treatment intensity [and marginal benefit gradually diminishes]. It is further assumed that treatment intensity is given and that there is a sufficiently large q_{max} such that $q \leq q_{max}$.

Decision-making occurs sequentially in three stages within the model (Figure A8.1). In the first date, Date 0, the health care payer selects a fraction μ *(1 - μ)* of the health care budget, B $(B > 0)$, to be allocated for acute intervention and long-term treatment. The objective function of the health care regulator is defined more precisely in the following section.

In the second date, Date 1, the hospital providing the acute intervention makes a decision between the available technologies 0, 1 and 2 and recognizes the associated costs. The technology choice of the hospital is constrained by the budget allocated to acute care.

Figure A8.1 Sequence of decisions



[12] This is consistent with the way the demand for long-termlong-term treatment is modelled. As the hospital faces no patients paying for their care out of their own pockets, it is natural to think that all revenue the hospital earns comes from a health care authority, a payer in our case. A purely public hospital would be a good real-world example.

In the last date, Date 2, the long-term treatment provider selects the level of treatment intensity, given the number of severely ill patients and the budget share chosen by the health care regulator. After receiving care at the long-term treatment provider the patient has achieved maximum potential for recovery given the initial severity and effectiveness of the given technology. (that is,, patients have d = *I*).

Since decision-making occurs sequentially in the model and decisions in later dates depend on choices made in early dates, the principle of the backward induction is applied: the model is solved in a backward fashion by first considering decisions made at the long-term treatment provider.

A8.1 Treatment intensity in the long-term treatment

The long-term treatment provider selects treatment intensity $q(\mu,t)$, which yields zero monetary payoff $L(q(\mu,t),\mu,t) = 0$. The zero profit condition can be solved with respect to unit cost as $c(q(\mu,t)) = \frac{(1-\mu)B}{(1-\tau_t)n}$. Since, by assumption, the unit cost function is monotonically increasing it has an inverse function $c^{-1}(z)$ for each positive average cost z. Hence the hospital will provide the level of treatment intensity $q(\mu,t) = c^{-1}(\frac{(1-\mu)B}{(1-\tau_t)n})$ and the associated total cost is given as $c(q(\mu,t))(1-\tau_t)n$. The treatment intensity in the long-term treatment provider decreases if the number of severely ill patients from the acute intervention, $n(t)$, increases or if the budget share allocated to the acute intervention, μ, grows. These results can be confirmed by taking partial derivatives of the zero-profit treatment intensity with respect to $n(t)$ and μ. As an example, consider the case in which the cost function is linear and $c(q) = cq$. This analysis yields optimal treatment intensity $q(\mu,t) = \frac{(1-\mu)B}{(1-\tau_t)nc}$, verifying the comparative static results of this example.

For a zero-profit provider operating under the fixed budget it is reasonable to assume that the provider decreases its long-term treatment intensity as the number of its patients increase. As the number of referred patients increase, the provider faces a higher cost but since a provider's revenue is fixed, it has to reduce its total cost by decreasing per patient treatment intensity accordingly.

A8.2 Selection of the acute intervention technology

The acute intervention provider's selection of technology is determined by the budget share μ chosen by the health care payer. If the payer selects a budget share which satisfies the condition $p_1 \geq \mu B \geq 0$, the acute intervention provider has no other choice but to use the minimum care technology and refer all its patients to the long-term treatment. The provider uses all its resources to generate organizational slack and $s = \mu B$. The efficacy of the intervention is at its minimum and the used technology is t_0. In case the payer provides more resources for acute interventions and $p_2 \geq \mu B \geq p_1$, feasible technologies are technology 1 and the minimum care technology. Because $0 = \tau_0 u_1 < \tau_1 u_1$, the acute intervention provider maximizes its utility by choosing technology 1 and spends any additional resources on organizational slack $s = \mu B - p_1$.

If the budget share for acute interventions satisfies $\mu B \geq p_2$ any one of three technologies is feasible for the provider. The assumption $1 > \tau_2 > \tau_1 > \tau_0 \geq 0$ implies that $n \tau_2 u_1 > n \tau_1 u_1 > n \tau_0 u_1 \geq 0$ and the provider ends up using the most effective and the most expensive technology, that is, technology 2. In this case the organizational slack is given as $s = \mu B - p_2$.

A8.3 The health care payer: slackness and allocating the given budget

In order to see which technology and what level of treatment intensity the health care payer is willing to implement, the payer's decision concerning the allocation of budget shares for the acute and long-term treatment at Date 0 is then analyzed. Three kinds of payers with different objective functions are considered. The first two payers are similar to each other as they both aim at minimizing the total cost of health care; the difference between the payers lies in their emphasis on different components of health care costs. The first type of payer aims at minimizing the total cost of health care, *CI*, defined as

$$CI = p_t + c(q)(1-\tau_t)n + s \qquad \text{(A8.3)}$$

The cost-minimization problem turns out to be easy to solve because of zero-profit constraints. The zero-profit condition for the acute intervention implies that $\mu B = s + p_t$. Moreover, as the long-term treatment provider also operates under the zero-profit condition and selects a treatment intensity which satisfies $(1-\mu)B$

= $c(q)(1-\tau_t)n$, the total cost to the health care payer for any budget allocation is $\mu B + (1-\mu)B = B$. This analysis suggests that the cost-minimizing payer is indifferent when it comes to allocating the health care budget between the acute intervention and long-term treatment units.

The second type of payer places a different weight on organizational slack than on other components of health care costs. A slack averse health care payer regards organizational slack as unproductive and attempts to root it out; a slack-inclined payer places special emphasis on promoting slackness.[13]

If the health care payer is slack-averse, it consequently aims to implement solutions for which organizational slack is as small as possible. This preference leaves the payer with three allocations to compare, namely budget allocations for which the acute intervention share μ obtains one of the values 0, p_1/B, or p_2/B. In each such point, the total cost of health care is B implying that the payer is indifferent for such points, as well as between these points randomly.

The third type of payer treats different components of health care similarly, but it takes benefits of health care into account. It is further assumed that the payer's goal is to maximize the difference between the health benefits and total costs of health care, to be called the net benefit of health care. As the organizational slack is a real cost-item for the payer it is included in the total cost of health care. The health utility from the acute intervention is given by the aggregate expected utility $EU(t) = n\,\tau_t\,u_1$ and the total benefit of the long-term treatment can be defined as $v(q)(1-\tau_t)n$. Consider a payer who selects budget shares of the acute intervention and long-term treatment by maximizing the net benefit of health care

$$NetBenefit = n\tau_t u_1 + v(q)(1-\tau_t)n - (p_t + c(q)(1-\tau_t)n + s) \tag{A8.4}$$

and shows no special preference for organizational slackness. By the zero-profit conditions it always holds true that $p_t + s = \mu B$ and $c(q)(1-\tau_t)n = (1-\mu)B$ and the total cost for the payer is B no matter how the budget shares are allocated between the acute intervention and the long-term treatment. Any differences that might arise between different allocations of the budget must come from differences in health benefits. In case the payer selects a budget share satisfying $0 \le \mu B \le p_1$, all patients are treated in the long-term treatment and the health care benefit is given as $nv(q(\mu,0))$, where $q(\mu,0) = c^{-1}(\frac{(1-\mu)B}{n})$, and the net benefit is given as $nv(q(\mu,0)) - B$. On

[13] An example of a slack-inclined payer is a government that wants to build excess capacity to guard against shortages in event of a public health crisis.

the other hand, if the budget share of the acute intervention satisfies $p_1 \leq \mu B \leq p_2$, then the net health benefit is $n[\tau_1 u_1 + (1-\tau_1)v(q(\mu,1))] - B$, where $q(\mu,1) = c^{-1}(\frac{(1-\mu)B}{(1-\tau_1)n})$. Finally if $p_2 \leq \mu B$, then the net benefit for the payer is $n[\tau_2 u_1 + (1-\tau_2)v(q(\mu,2))] - B$, where $q(\mu,2) = c^{-1}(\frac{(1-\mu)B}{(1-\tau_2)n})$. Clearly, as the total cost of health care is always the same, the health care payer implements a technology and treatment intensity for which the per patient health benefit $\tau_t u_1 + (1-\tau_t)v(q(\mu,t))$ is as high as possible. Based on the above analysis two proposition sets are offered.

Proposition 1: *Because the providers operate under the zero-profit constraints,*

a) *A payer interested in minimizing the total cost of health care is indifferent between different allocations of the health care budget*
b) *A slack-averse health care payer is indifferent between budget allocations yielding zero organizational slack, and*
c) *A health care payer interested in the net benefit of health care bases the decision-making on per patient health benefits only.*

A8.4 Social optimum

The socially optimal health care technology and the level of treatment intensity is analyzed next. In order to do that, consideration is paid to a social planner who maximizes the welfare function

$$W(t,q) = n\tau_t u_1 + (1-\tau_t)nv(q) - p_t - (1-\tau_t)nc(q) \quad \text{(A8.5)}$$

The welfare function takes into account the total health benefits and total cost of health care. As the organizational slack is basically a transfer of income from the regulator to the provider, the slack from the welfare analysis is ignored.

The social planner maximizes welfare by selecting a technology from the set of available technologies and the level of treatment intensity. A socially optimal technology and treatment intensity (t^*, q^*) must satisfy the condition

$$W(t^*,q^*) \geq W(t,q) \quad \text{(A8.6)}$$

for all feasible treatment intensity and technology pairs $(t,q) \in T \times R$.

Assuming that socially optimal treatment intensity exists and is interior, it must satisfy the necessary condition for maximum

$$v'(q^*) - c'(q^*) = 0 \tag{A8.7}$$

Socially optimal treatment intensity equates patient level marginal benefit from the long-term treatment with the marginal cost. What is worth observing is that the socially optimal long-term treatment intensity is independent of the optimal acute intervention technology. A socially optimal acute intervention technology t^* satisfies the condition

$$n\tau_{t^*}u_l + n(1-\tau_{t^*})v(q^*) - p_{t^*} - n(1-\tau_{t^*})c(q^*) \geq n\tau_t u_l + n(1-\tau_t)v(q^*) - p_t - n(1-\tau_t)c(q^*) \tag{A8.8}$$

where t is any feasible technology in the set of available technologies. The above condition can be rearranged as

$$n\left[u_l(\tau_{t^*} - \tau_t) + V(q^*)(\tau_t - \tau_{t^*})\right] \geq p_{t^*} - p_t \tag{A8.9}$$

where $V(q^*) = v(q^*) - c(q^*)$ is the net benefit from treating one patient in the long-term treatment, evaluated at the optimal treatment intensity q^*.

The first part on the left hand side of the inequality (Equation 10) denotes the net benefit offered by the optimal technology as opposed to any alternative health care technology, where the benefit is described by a change in the probability τ of having only a mild disease after an intervention with the optimal technology. The second part describes the marginal cost change induced by an optimal technology, where the cost change is described by a change in the number of severely ill patients entering long-term treatment after an intervention using optimal technology. The sum of these must be greater than the price of changing to optimal technology. It is to be noted that any of these terms can also be negative.

The above condition can be rewritten as

$$n\left[u_l - V(q^*)\right](\tau_{t^*} - \tau_t) \geq p_{t^*} - p_t \tag{A8.10}$$

In the above inequality (Equation 11), the left-hand side measures the incremental total benefits between the efficient technology t^* and its alternative technology t and the right-hand side of the inequality measures the incremental cost incurred from a change from technology t^* to t. For example, if the more effective

technology 2 is chosen instead of technology 1 (and the difference $\tau_2 - \tau_1 > 0$), the expected aggregate utility from acute intervention increases, and the number of severely ill patients being referred from the acute intervention to the long-term treatment will consequently be reduced.

The term $u_1 - V(q^*)$ denotes the total benefit a patient receives from health care. The reason why the net benefit $V(q^*)$ enters equation 11 with a negative sign is that a more effective acute intervention technology reduces the number of patients who would enjoy the net benefit $V(q^*)$ at the long-term treatment in case of a less effective technology.

For the sake of simplicity it is assumed throughout the following analysis that the patient utility of the acute intervention, u_1, exceeds the net benefit of long-term treatment, $V(q^*)$, when evaluated at the optimum, or $u_1 - V(q^*) > 0$. For notational streamlining only in the following analysis the total aggregate benefit from health care is denoted as $n[u_1 - V(q^*)] = W$.

As a final step in the model the preconditions for each specific technology to be optimal technologies for society are derived.

Conditions for technology 2 to dominate

First, the conditions under which the socially optimal health care technology is technology 2 are analyzed. This outcome occurs if technology 2 is better than technologies 1 or 0. As $\tau_2 - \tau_1 > 0$, assuming[14] here $\tau_0 = 0$ and $p_0 = 0$, the formal conditions for a social planner to choose technology 2 are given as

$$W \geq \frac{p_2 - p_1}{\tau_2 - \tau_1} \qquad \text{(A8.11)}$$

denoting the comparison against technology 1, and

$$W \geq \frac{p_2}{\tau_2} \qquad \text{(A8.12)}$$

denoting the comparison against technology 0.

Equation A8.12 says that the total aggregate health benefit exceeds the incremental cost-efficiency ratio between technologies 2 and 1, respectively, and the condition (13) does the same except that it compares technology 2 to technology 0.

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[14] We set $\tau_0 = 0$ so that the model compares a new technology to a baseline technology, looking at incremental changes.

Both conditions hold true simultaneously if the total aggregate health benefit exceeds both incremental cost-efficiency ratios, that is, the condition $W = \max\left[\frac{p_2 - p_1}{\tau_2 - \tau_1}, \frac{p_2}{\tau_2}\right]$ is satisfied. Now, $\frac{p_2 - p_1}{\tau_2 - \tau_1} \geq \frac{p_2}{\tau_2}$ holds true if and only if the condition $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1} > 1$ is satisfied. In this case a sufficient condition for the planner to prefer technology 2 is when $W \geq \frac{p_2 - p_1}{\tau_2 - \tau_1}$. In case the condition $\frac{\tau_2}{\tau_1} \geq \frac{p_2}{p_1} > 1$ holds true, technology 2 should be chosen whenever the total health benefit exceeds the incremental cost-efficiency ratio for the minimum care technology, or $W \geq \frac{p_2}{\tau_2}$.

Conditions for technology 1 to dominate

The situation in which technology 1 is socially optimal is considered next. Since $\tau_1 - \tau_0 = \tau_1 > 0$ and $\tau_2 - \tau_1 > 0$, the conditions for technology 1 to dominate over other health care technologies occurs when conditions

(A8.13) $$W \geq \frac{p_1}{\tau_1}$$

and

(A8.14) $$\frac{p_2 - p_1}{\tau_2 - \tau_1} \geq W$$

are both satisfied. Technology 1 is optimal for society if and only if the total health benefit satisfies the condition $\frac{p_1}{\tau_1} \leq W \leq \frac{p_2 - p_1}{\tau_2 - \tau_1}$ that is, technology 1 is better than technology 0 and technology 2. If $\frac{p_2 - p_1}{\tau_2 - \tau_1}$ is smaller than $\frac{p_1}{\tau_1}$, the above conditions cannot be satisfied and technology 1 cannot be socially optimal. This situation occurs if the condition $\frac{\tau_2}{\tau_1} > \frac{p_2}{p_1} > 1$ holds true.

Conditions for technology 0 to dominate

Since $\tau_t > 0$ for $t = 1,2$, the social planner wants to select the minimum care technology at the acute intervention if and only if

$$W \leq \frac{p_t}{\tau_t} \qquad \text{(A8.15)}$$

for $t = 1,2$. The above two conditions hold simultaneously when the condition $W \leq \min\left[\frac{p_1}{\tau_1}, \frac{p_2}{\tau_2}\right]$ holds true. Now $\frac{p_2}{\tau_2} \geq \frac{p_1}{\tau_1}$ if and only if $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$.

Choosing the technology

The relationship between the ratios $\frac{p_2}{p_1}$ and $\frac{\tau_2}{\tau_1}$ plays an important role in ranking the incremental cost-effectiveness ratios (ICER) for the technologies. The condition $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$ is crucial in ranking the cost-effectiveness ratios between different technologies. The cost-effectiveness ratio for two technologies, t and s, are denoted as $ICER_{ts} = \frac{p_t - p_s}{\tau_t - \tau_s}$. Under the condition $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$ it holds true that $ICER_{10} \leq ICER_{20} \leq ICER_{21}$, and $\frac{p_2}{p_1} < \frac{\tau_2}{\tau_1}$ if the condition does not hold true and then $ICER_{21} < ICER_{20} < ICER_{10}$.

The following conclusions ensue:

1. If the relative price increase of switching from technology 1 to technology 2 is greater than the relative increase in probability of low severity, that is, the condition $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$ holds true, then the incremental cost-effectiveness ratios can be ranked as $\frac{p_2 - p_1}{\tau_2 - \tau_1} \geq \frac{p_2}{\tau_2} \geq \frac{p_1}{\tau_1}$. In this case, technology 2 is socially optimal if the total aggregate health benefit $n\left[u_l - V(q^*)\right]$ exceeds the highest incremental cost-effectiveness ratio $\frac{p_2 - p_1}{\tau_2 - \tau_1}$, technology 1 is socially optimal if

$\frac{p_2 - p_1}{\tau_2 - \tau_1} > n\left[u_l - V(q^*)\right] > \frac{p_1}{\tau_1}$, and the minimum care technology is socially optimal in case $\frac{p_1}{\tau_1} \geq n\left[u_l - V(q^*)\right]$.

2. If the relative increase in probability of health offered by technology 2 is equal to, or higher than, the relative price increase albeit technology 2 is more expensive than technology 1, that is, $\frac{\tau_2}{\tau_1} > \frac{p_2}{p_1} > 1$, then technology 1 is never socially optimal. Consequently, technology 2 is preferred by the social planner if

(A8.16) $$n\left[u_l - V(q^*)\right] \geq \frac{p_2}{\tau_2} \Leftrightarrow \tau_2 n\left[u_l - V(q^*)\right] \geq p_2,$$

that is,, the total benefit offered by technology 2 is considered greater than its price. Technology 0, minimum care technology, is optimal otherwise. The following proposition summarizes the above discussion.

Proposition 2: *If* $\frac{p_2}{p_1} \geq \frac{\tau_2}{\tau_1}$ *then technology 2 dominates under the condition,*

$n\left[u_l - V(q^*)\right] \geq \frac{p_2 - p_1}{\tau_2 - \tau_1}$ *technology 1 dominates under the condition,*

$\frac{p_1}{\tau_1} \leq n\left[u_l - V(q^*)\right] < \frac{p_2 - p_1}{\tau_2 - \tau_1}$ *and technology 0 dominates otherwise. If*

$\frac{\tau_2}{\tau_1} > \frac{p_2}{p_1} > 1$, *then technology 2 dominates under the condition* $n\left[u_l - V(q^*)\right] \geq \frac{p_2}{\tau_2}$ *and the minimum care technology, dominates otherwise.*

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CHAPTER 9

IDEAL DOMESTIC CLUSTERS IN THE GLOBAL VALUE CHAIN

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This final chapter offers a dynamic framework for the realignment of overall innovation action plans and corporate strategies. Drawing from the earlier chapters, literature on international trade, interviews of 89 business leaders, and seminar discussions within academia, government, and industry in Finland and the USA we formulate two clusters within the Finnish biotechnology industry, and offer a recommendation for policy change in line with our findings.

9.1 Biotechnology within a small open economy

Trends in global population demographics reflect new extremes and widening gaps based on geography and level of industrialization. Developing countries in Africa show high birth rates and low life expectancies, a development severely aggravated by HIV, whereas Western Europe's population is diminishing and aging, leading to a potentially severe decline in the workforce, which could threaten production. In addition to straining retirement systems, the aging of the population in Europe will curtail the supply of public health care and potentially raise associated costs. New technologies could play an important role in limiting cost increases by providing new, cost-efficient health care applications. Additionally, biotechnology applications for functional food might promote positive health outcomes, further limiting costs associated with particular diseases through prevention.

Another economic disruptive factor is that globalization has entered its third stage, with research and development (R&D) functions being relocated to devel-

oping countries such as China and India. With this global outsourcing of R&D, knowledge tends to flow away from the original locations of specific innovations. This trend raises a central question for the Western technology industry: are we able to offer sufficient incentives for global players to anchor innovative R&D in Western countries, and thereby catch the upside potential in a globalizing and service-oriented world?

Many believe that we are only in the earliest phase of creating knowledge-intensive, high-technology solutions to global phenomena. Technology-orientation and digitalization are assumed to expand to all areas of life, largely through integration with life-science-based innovations. In line with this assumption, *ubiquitous computing* and *hybrid society* are expressions used to describe our future.

Biotechnology is one of the primary underpinnings of a technology-oriented world. As such, extensive subsidies and support have been offered toward the creation of biotechnological research and commercialization programs in Western countries. But a key question remains: are the resultant programs based on the regional strengths of the distinct countries? This question is especially important because small open economies lack the critical mass to do everything themselves, implying a need for international and regional specialization.

In a small open economy, such as some of the US states or European regions including all the Nordic countries, industry specialization could provide a pathway to success through international trade to boost regional growth. Moreover, the Nordic welfare system seems to be able to provide a competitive advantage through supporting sustainable technology development. Particularly, a one-payer highly advanced health care system could be steered in a way that provides benefits for both the health care system and industry.

9.2 Analytical background of the strategic initiatives

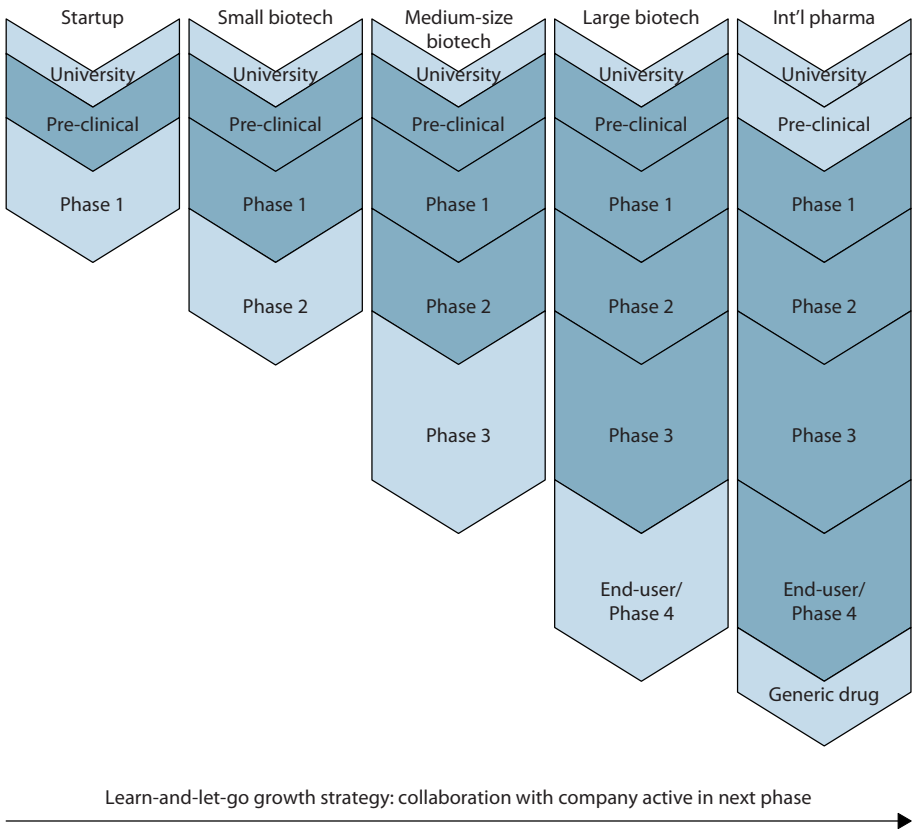
The key factor for any new biotechnology company is to find its niche within the global value chain, where the pharmaceutical giants are struggling with the combination of a scarcity of block buster drugs that could replace those with patents expiring on one hand, and clear trends towards personalized medicine on the other. In this changing world a start-up company can screen targets for the R&D process of a large multinational company, or the start-up can serve large companies by organizing clinical trials or by building a production facility with the capability to biologically produce pharmaceuticals. All of these above niches can generate positive cash inflows that the new companies can use to gradually extend their activity to preclinical or clinical phases, and thereby position themselves between

two extremes of commercialization strategies: to grow in either scope or scale of activities.

In the scope based growth strategy, the company takes over other parts of the value chain by utilizing learning through collaborative methods and generating new applications needed in the market (Figure 9.1). In the scale based growth strategy, the company deepens its expertise in the strictly defined part of the value chain and thereby enlarges its market share in the chosen niche market (e.g. biological production) by providing higher quality services or lower costs. In a sequential strategy the company can first specialize in a narrow niche and then widen its scope to other parts of the value chain.

We put the discussion above into a geographical context by comparing two regions with similar populations and activity levels but highly different market

Figure 9.1 Growth of drug development company applying learn-and-let-go strategy



structures: Finland and the state of Illinois, USA. There are about 80 active health care biotechnology companies in both states. However, significant volumes of R&D and production activity of five giant pharmaceutical companies are located in Illinois, whereas Finnish companies are of small and medium size. We claim that a prosperous conduct and fruitful collaboration between the states could arise from these differences between the market structures.

In Illinois the critical mass of biotechnology companies cannot provide a sufficient basis for developing new applications, and hence the domestic large companies need to utilize applications generated by biotechnology companies also outside of the state. Simultaneously, Finnish biotechnology companies search for international distribution channels in order to reach the global marketplace. In this setting, both regions have to find their competitive advantage and clearly communicate it to respective stakeholders: how to utilize the complementary competencies and potential benefits arising from collaboration between these regions.

Big companies could utilize the homogeneity of the Finnish population and gene banks in their search for new biological causal relationships explaining disorders and disclosing new potential remedies. However, also the heterogeneity of the Illinois population generates some particular advantages, such as providing a more variable gene base for clinical trials and a test market for the USA as a whole.

In this section we construct a dynamic framework to serve as a tool in assessing the present situation and creating possible new strategies that include also the government. Our framework draws from the literature on international trade as outlined in the following subsections.

9.2.1 Comparative advantage

Ricardo's concept of comparative advantage serves as the foundation of trade analysis and as a basis for further modeling tradition. For instance, the Heckscher-Ohlin-Samuelson approach links the regional factor proportions and their productivity to the comparative advantage of regions (Heckscher and Ohlin, 1919; Samuelson, 1986). There have been an extensive number of theoretical contributions and empirical investigations both to the Ricardian and the Heckscher-Ohlin-Samuelson modeling tradition up to the present day. According to the trade literature, all trading regions will gain if each region specializes in production at a lower opportunity cost than other regions. According to the Heckscher-Ohlin model a region benefits if it increases its production of goods manufactured from regional resources that are relatively abundant, especially when trade barriers are lower.

A small open economy has limited resources. In order to gain a competitive advantage, it is necessary that economies specialize in specific application areas or areas utilizing relatively abundant production-related resources. The concept of comparative advantage inherently influences both business and regional trade strategies.

Concept 1: There will be overall economic gains within a free trade area if an industry utilizes a resource combination that is relatively abundant domestically.

9.2.2 Market structure and spatial agglomeration

Krugman and Venables have emphasized a new geography-based approach to economic analysis (Krugman, 1991; Krugman and Venables, 1995; Venables, 1996). Specifically, they analyzed how market structure is related to the location of economic activities. Their modeling of market structure was based on Chamberlin-type monopolistic competition as presented by Dixit and Stiglitz (1977). The primary goal of the original analysis is to show that higher sunk costs in industrial production (e.g., higher M&A or R&D costs) are associated with more differentiated products for consumers. At one extreme, there would be only a few producers with greatly differentiated products. At the other there would be an infinite number of low sunk-cost producers, in a scenario in which the consumer prefers a large variety of less differentiated products.

Krugman extends the model of monopolist competition to the context of spatial structures (Krugman, 1991). In the geographic centre-periphery model there are three market features affecting spatial structures:

1. Increasing returns to scale in a manufacturing sector are related to higher sunk costs associated with production processes. This, in turn, promotes the strengthening of the geographic center-periphery structure.
2. The higher the sector's usage of available production factors, the more a centre-periphery structure gains strength. This effect implies that firms benefit from a local concentration of labor (or other factors) and individuals seeking employment incur lower costs due to the geographic concentration of companies.
3. Lower trade barriers or lower trade costs imply a tendency towards the spatial agglomeration of a sector showing increasing returns to scale in its production process. The firms can also subcontract with each other locally, with relatively low coordination (e.g., transport of inputs) costs (Krugman and Venables, 1995; Venables, 1996).

Geographic economics stresses the importance of market structure, for example, economies of scale, which can be related to the efficient allocation of resources.

Concept 2: Small open regions can attract international companies if there is a critical mass of location-specific but globally scarce resources available in the region.

9.2.3 The Infant Industry Argument

In the 19th century Hamilton and List argued for public support of infant industries in order to achieve an advantage over other countries (Krueger and Tuncer, 1982; Shafaeddin, 2000). The infant industry argument (IIA) is based on the temporary need for protection (or support) of an infant industry if the industry is unable to grow in the international context of free trade and foreign rivals. The initial excessive costs of such industry support are assumed to be compensated for by the later stages' surplus profits and economic growth, returns that could not have been captured without initial governmental support. However, IIA has been miscast as an argument for exceedingly long-term protection, which was not its framers' original intent.

There are some basic arguments that provide a rationale for directing supporting activities at infant industries, such as cumulative learning within the infant industry through the creation of positive externalities. The potential externalities over time include, for example, availability of technically competent labor, technological spillovers, and diminishing transport costs due to the creation of a local cluster. If these externalities could be created only through governmental promotion, and if the long-term GDP effects exceeded the initial short-term costs of the promotion, it would be reasonable to provide temporary support for an infant industry. Thus the infant industry argument diverges from the static trade restriction schemes which protect domestic industry through permanent import tariffs or quotas, or by other long-term means.

A small open economy cannot afford to produce all products itself, but it could gain from the creation of a critical mass in some niche markets. The infant industry argument stresses the importance of subsidizing application areas that are incapable of becoming globally competitive on their own. The temporary aspect of the subsidies is, however crucial, irrespective of what forms they take (e.g. tax privilege, corporate subsidy, other forms of government funding).

Concept 3: Short-term government support to strengthen emerging critical resources within an infant industry aims to promote positive externalities and an economic upside in the long term.

9.2.4 Cluster dynamics

Porter (1990) concludes the discussion on spatial competitiveness with a discourse on industries' ability to create incremental and radical innovations. In Porter's diamond model, innovation intensity depends on the interaction among four attributes:

1. Factor conditions
2. Demand conditions
3. Related and supporting industries, and
4. Market structure.

Skilled labor and a well-developed infrastructure are critical factors for production and innovation; if there are demanding, sophisticated customers in the domestic marketplace, companies are forced to be innovative. An internationally competitive supporting industry is crucial to the availability of cost-effective inputs. Competitive domestic markets with innovative rivals intensify the innovation processes, and reinforce the development of first-mover strategies.

Concept 4: The interaction of highly specialized resources, sophisticated domestic customers, internationally competitive supporting industries, and intense domestic competition creates an innovative, competitive industrial cluster.

9.3 Synthesizing the theories into a dynamic framework

The four central concepts presented above have traditionally been viewed as mutually exclusive. However, we believe there is significant value in fusing even seemingly contradictory frameworks or sectors into a more comprehensive framework. As the biotechnology industry extends well into global markets, it seems logical to focus on the value of combining central frameworks derived from the literature of international trade.

In line with this goal, we first analyzed the components of the frameworks with special focus on potential implications for the biotechnology industry. The combination of the implications can be stated as follows:

Concept 5: Create a relatively abundant (regionally), location-specific, globally scarce interactive combination of

A. Unique factors of production and infrastructure

B. Demand-driven commercialization strategies

C. Internationally competitive supporting industries

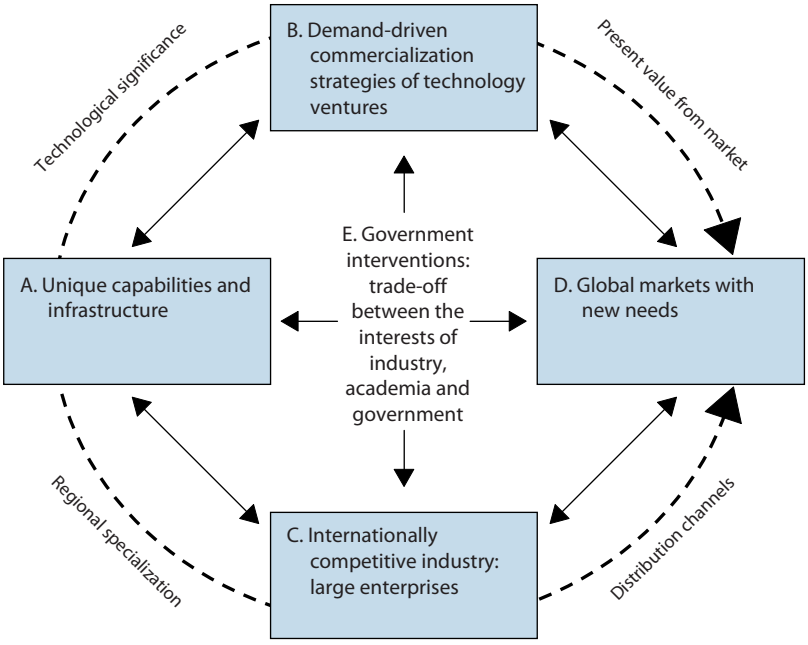
D. Access to global markets reflecting new user needs.

by strengthening temporarily those parts of the infant industry critical to long-term growth and success. To this end, aligned interests should be created between industry, academia, and government.

Next we unified the chosen frameworks by introducing a dynamic aspect that linked them seamlessly to one another. We combine implications from the international trade literature and a Porterian diamond model to the four attributes in Figure 9.2. Our framework also includes a strategic aspect. It proposes that regional economies start with unique (regional) factors of production and target global markets by collaborating with supporting industry via sequential and clearly communicated business strategies in line with their application segments.

The developed framework places our findings in the context of a small, open

Figure 9.2 Sustainable Technology Development Platform



Source: Porter, 1990; Hermans and Kulvik, 2006a; 2006b.

economy's innovation system as it faces global markets in two regards. First, technologically significant and economically valuable intellectual property rights provide a base for the construction of a business strategy to exploit the sophisticated domestic markets in forging a pathway to the global markets. Second, regional specialization of commercialization activities can provide a critical mass of competencies that serves as a base for specific industrial clusters. If the infant biotechnology industry could provide complementary competencies and earning prospects for more mature industries in the future, these could justify financing and facilitating the development of the infant biotechnology industry.

A demand-driven commercialization strategy is a prerequisite for any further success in biotechnology development – global markets with new needs are the primary incentive for any R&D strategy (D→B→D in Figure 9.2). A real-life example is Gilead Sciences, Inc. which in 2003 launched its Gilead Access Program for introducing the HIV/AIDS to developing countries such as those in Africa, where up to 30% of population have HIV. Since then, Gilead's market capitalization has risen from $7.8 billion at end of 2002 to $51 billion in August 2008.

A company can commercialize its technology venture through an alliance (A→B→C→D in Figure 9.2) or by straight access to the global market through out-licensing or product launch (A→B→D in Figure 9.2). However, a commercialization of a high market potential technology, as opposed to a niche product or an orphan drug, requires vast amounts of resources and marketing skills. Even with a promising new technology the company can run into critical resource scarcity in supplying the product for the global market. An example of such scarcity is found in the commercialization of the recombinant DNA drug etanercept, offered by Immunex under the trade name Enbrel. Immunex corporation ran out of manufacturing capacity and could not meet the great demand generated by the global markets (Krishnan, 2002). This challenge was overcome by Immunex' merger with Amgen.

Although large pharmaceutical companies use billions of dollars annually for their R&D activity, they are constantly looking for external R&D collaborators (C→B→C→D in Figure 9.2). A lower level of internal R&D activity enables intensive utilization of the collaboration network of small and medium-sized biotechnology companies. Such collaborations are useful for biotechnology companies needing resources, as well as a large international company since it can outsource initial stage drug development with high risks for failure. We find an example in Millennium Pharmaceuticals Inc., an active partner with several large drug companies. The intensive partnering has also been successful for Millenium: its market capitalization exceeded $5.3 billion the day before Millenium was acquired in a tender offer by Takeda in May 2008 at a valuation of $8.8 billion (Solf et al., 2002, Takeda-Millenium, 2008).

The company may construct its commercialization strategies according to product groups and distinctive market segments. For example, Vertex Pharmaceuticals has utilized alliances with other companies in developing drugs with high market potential, and with patient organizations regarding drugs with smaller market potential (e.g. orhan drugs). They have also started development projects without an external partner. By combining alliances (A→B→C→D in Figure 9.2) and independent commercialization strategies (A→B→D in Figure 9.2) Vertex has applied a sequential commercialization strategy (Lief et al. 2008).

9.4 Applying the model: Finland as a case study

This section begins with a short description on earlier findings on the Finnish biotechnology industry. Then the dynamic framework is applied on two health care innovation clusters, one local that already exists and one national that we suggest to be developed.

The Tampere region biomaterials cluster is analyzed both for demonstration of the framework and in order to seek for additional opportunities within the existing cluster. The second example proceeds to construct a potential bio-information based pharmaceutical cluster, and the virtual cluster is viewed from the point of each separate stakeholder. Finally, policy recommendations to government are drawn.

9.4.1 The Finnish biotechnology playground

Our "test laboratory", Finland, has been rated one of the top countries in international competitiveness (IMD, 2004; WEF, 2005; WEF, 2006; WEF, 2007; WEF, 2008). Despite this, Finland does not attract investments, is not a leader in terms of standards of living, and is unable to significantly reduce its high unemployment rate; this has been described as the *Finnish paradox* (Kuusi and Hautamäki, 2005). Furthermore, Finland has been strongly affected by shifts within its demographics through its large ageing post-war generation.

The business leaders of 89 Finnish biotechnology companies representing more than 85% of the entire Finnish SME biotechnology sector were interviewed in a unique survey by ETLA in 2005. The results showed that biotechnology leaders see scientific competencies (A in Figure 9.2) as a necessary but not sufficient factor in global success in biotechnology (Hussi et al., 2006). In contrast to Finland, many European countries and the US have a pool of managers, also from the pharmaceu-

tical industry, and venture capitalists with biotechnology expertise have brought business skills to the companies in their portfolios.

The Finnish biotechnology business leaders also called for mechanisms through which business experience from more mature industrial branches (C in Figure 9.2) could be transferred to new biotechnology companies. In accord with this, Hermans and Kulvik (2006a; 2006b; 2007) suggest forming clusters that target application areas attracting large industrial branches instead of focusing on a specific biotechnological development. If well-established industrial sectors can see potential in new applications offered by biotechnology, the companies could contribute more than financing, for example, supporting the development of business strategies and international distribution channels.

Nikulainen et al. (2006) detailed how Finnish biotechnology companies relate their innovations' technological significance, in terms of backward patent citations, to the company's present value. The analysis indicates that the most technology-oriented companies have the highest expectations of future sales levels. This finding is supported only in part by empirical studies of foreign markets: these investigations show a stronger link between *forward* citations and the companies' economic value. The link indicates that international markets value the companies more highly if their protected technological knowledge is cited by other companies in their own patenting activity, suggesting that the technology is appreciated by the focal companies' peers.

This finding can be closely related to Luukkonen's (2005) finding that companies in distinctive application segments exploit differing organizational forms and, therefore, divergent strategic models (B in Figure 9.2). As alluded to in our strategic framework, infant companies, on one hand, can utilize networks to learn how to develop their products closer to the marketplace even under strict governmental regulation; and companies in mass market businesses such as energy applications, which have a lower degree of governmental regulation than pharmaceuticals and biotechnology, can, on the other, use vertical integration as the most efficient vehicle for entering the global market. In terms of IPRs, companies with several patents in high-tech areas could benefit from a collaborative strategy, whereas firms with a less significant patent portfolio might want to choose a more comprehensive in-house approach for their R&D and marketing efforts.

Hermans and Tahvanainen (2008) argued that regional specialization patterns matter. If there are regionally specialized unique factors of production (A in Figure 9.2), the region could provide a sufficient critical mass and, consequently a comparative advantage. This should attract external financing and act as a vehicle for industrial clustering (C in Figure 9.2). A well-developed industrial cluster can breed flourishing subcontractor-customer relationships and thereby maintain expertise-

rich and highly sophisticated domestic markets (D in Figure 9.2), a prerequisite for global success.

As argued by Hussi et al. (2006), many Finnish research-oriented and technologically advanced biotechnology companies lack business expertise. An intensive producer-user relationship could offer companies a unique opportunity to better understand the needs and requirements of domestic but world-leading customers. By serving these sophisticated domestic customers, companies could accrue marketing experience that could subsequently be exploited on a larger scale by entering global markets.

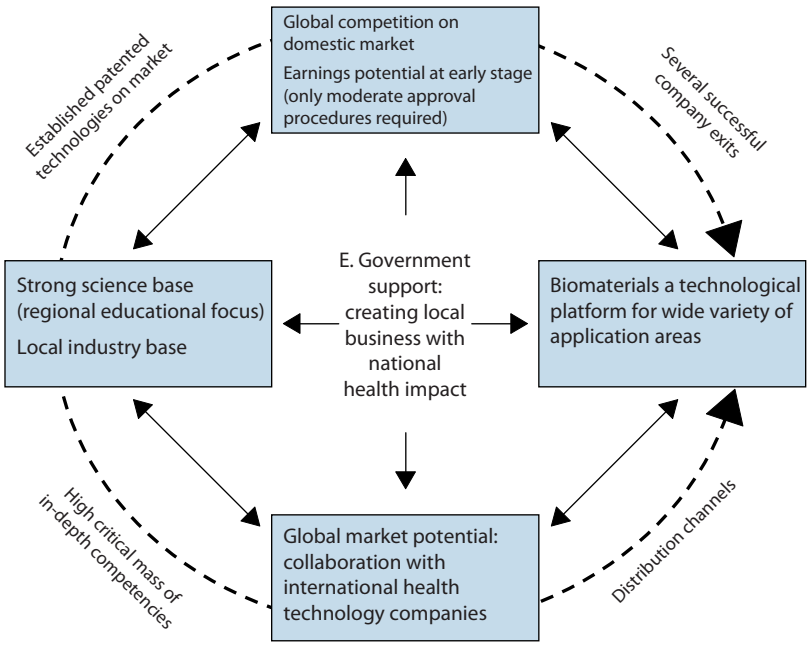
9.4.2 The biomaterials cluster

Tampere has become a centre for biomaterial related science and R&D. Two nationally significant exits have shown the vitality of this regional cluster, and the vested knowledge serves as a basis for knowledge spillovers to new businesses in the region. Moreover, the region has been able to build an educational focus around biotechnology that streches over traditional institutional boundaries. Thus the Tampere region has **unique capabilities and infrastructure** in biomaterials: a strong science base with a regional educational focus, and a strong industry base (see Figure 9.3).

The highly specialized market for biomaterials is global, and reciprocally the biomaterials companies face from start global competition. Due to this international nature of the biomaterials technology as well as the advanced stage of Finnish research and healthcare, the domestic market is both demanding and knowledgeable. In addition to market testing, the collaboration with domestic top-notch clinics and university hospitals could provide opportunities to find new application areas for biomaterials; a close contact with domestic customers enables companies to understand the customer needs. By close cooperation the companies can receive a concise feedback already at an early stage of product development: the global markets are represented though entities "just around the corner".

By binding [local] scientists and scientific opinion leaders both as company staff and on advisory boards and offering them full access to the respective companies' new applications, the researchers' and opinion leaders' networks can be utilized both for intensive R&D activities and international promotion of the products. Moreover, despite strict regulation the time span from invention to market is clearly shorter in biomaterials than in drug development -our second example. Local customers that are all under the same legislation open an opportunity for a strategy of early stage earning potential, yielding true income so strongly emphasized by capital investors.

Figure 9.3 The biomaterials cluster



A **demand-driven commercialization strategy** for product development up to the end-user market can be expressed: early feedback from knowledgeable customers and research entities running under an identical regulative environment, and early stage earnings potential.

The Tampere biomaterials cluster has already shown exits both as IPOs and through international financiers or acquisitions by other companies. Furthermore, the local knowledge and networks in electronics and software programming can be utilised in biomaterial related projects. Life sciences could provide many application areas that could be attractive in the eyes of related industries.

However, there seems to be a lack of domestic industrial fields that would have a resource-based or market-oriented close link with the development of biomaterial applications. This could imply that the most promising companies might eventually be taken over by multinational companies active in the application area. This is in the interest of original shareholders, but not necessarily in the interest of government if the companies thereby are relocated otside the country.

Irrespective of ownership issues the global market potential calls for sufficient investment capacity, large distribution channels and a broad knowledge base on international marketing; resources that small biotechnology companies can not present. Consequently, in order to become an internationally competitive industry **the presence and cooperation of large enterprises is needed**.

If the local cluster holds a critical mass it could provide tempting technology transfer opportunities and an attractive labor pool for the incoming foreign owner. In such a case there would be a clear incentive for the acquiring company to preserve the smaller [Finnish] company (Haspeslagh and Jemison 1991). The strong locally specialized industrial setting can thus become a pathway for acquiring critical [foreign] resources.

Global markets with new needs. Cell and tissue engineering is a rapidly accelerating field utilising especially biomaterials and biomedical technology. Practical applications have ranged from frontal sinus implants correcting chronic inflammation to *in vivo* cultivated biosynthetic jaw pieces for correcting post-cancer deficiencies. Cell and tissue engineering can be seen as a generic technology with a multitude of application areas.As the results of the research and development can have a clear impact also on society level, the potential impact is global.

A small company with limited resources can keep pace with the development frontier in its focus area. However, new applications can come from a broad spectrum of fields, even far outside the specialized company's original intentions but with a significant synergistic potential in technological applications. Moreover, the technology might offer a significant advantage as part of a larger entity that as a whole is outside the original company's area of focus. Close cooperation both with local top-notch units and global players opens the channels for crucial market feedback and thereby the potential to catch new market opportunities.

The government as interventor and facilitator. Biomaterials have been one of the major technological focus areas of the Finnish innovation system. As a result, the institutions involved have gained both technological and financial knowledge. The state support has strongly emphasized cooperation with universities and private clinical units, and hence the actors face well-educated and challenging customers locally.

Besides promoting the creation and prosper of a local industry, the government has incentives also from a broader aspect: to support business that can have a national health impact. The Finnish healthcare system has repeatedly been regarded as one of the most efficient (Kotzian, 2008; Kotzian, 2009). As technology forms a central part of modern healthcare, the government has strong incentives to support the Finnish healthcare system to remain at the forefront of efficient medical technology.

Moreover, the government can guide development to bridge the gap between short term benefits and long term sustainable development. For a small open economy the key is to promote local strenghts in a global context, lowering any barriers for international cooperation and discarding protective attitudes.

9.4.3 A bio-information-based pharmaceutical cluster

We will now introduce a potential new cluster and asses it through our dynamic framework. The cluster focuses on drug development and diagnostics, and would be built on Finland's unique patient databases, the applications of which have been aimed at controlling the rising costs of health care. We will use the sustainable technology development platform in Figure 9.2. as an initial starting point.

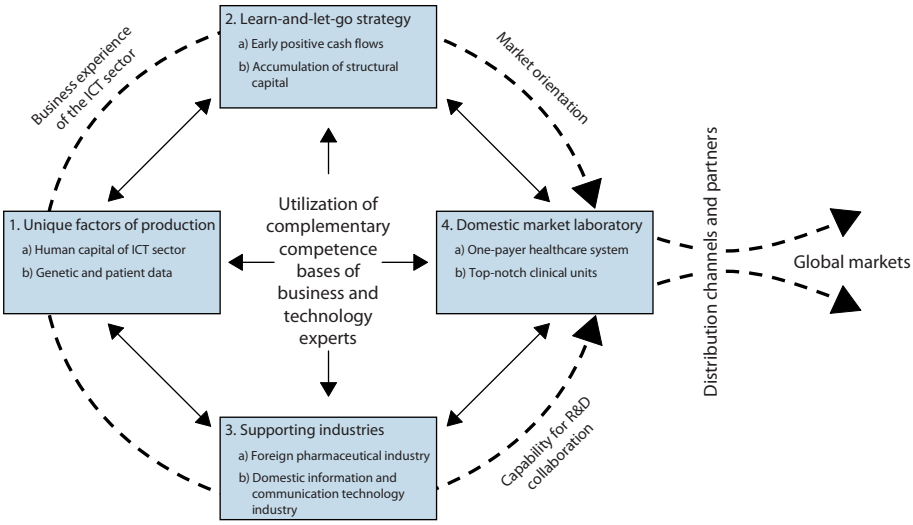
Unique factors of production in Finland

The most prevalent diseases have influenced the allocation of Finnish research resources, which has led to the development of internationally significant areas of expertise in medical science and related fields. Also, Finland's one-payer health care system has facilitated a comprehensive patient case record scheme which, combined with the rating of numerous clinical institutes as Centres of Excellence, creates a unique base for biotechnology development in Finland (Eskola, 2005). The research knowledge, along with increasing demand for its commercial applications (especially as related to the aforementioned national diseases), enables the use of the domestic market as a commercial test market. Cooperation with end users of health care products facilitates the product development of biotechnology companies and the development of service concepts, and also prepares companies for entering the highly competitive international markets.

Applying our strategic framework yields the following conceptualization of a Finnish health care cluster (Figure 9.4):

1. In our conceptualization, Finland could offer select content from domestic patient data banks to [international] pharmaceutical companies. However, the data offered would be specified to cover only a circumscribed application area. The original data banks would remain the property of Finland.
2. Research using the data must be performed in Finland, in collaboration with entities controlled by a government institution or the equivalent. This would be stipulated in legislation in concordance with the original purpose of the data bank: to promote and enhance the well-being of Finnish

Figure 9.4 The bio-information based pharmaceutical cluster



citizens. All knowledge spillovers would also remain the property of Finland.

3. If the data banks and knowledge are as valuable as assumed, even such a limited release of their data should attract international pharmaceutical companies to establish research partnerships with Finnish entities. The establishment of a research cluster with strong ties to the international pharmaceutical industry would be a strong positive signal to investors, and the infusion of knowledge would also offer a means for reducing the present disadvantageous information asymmetry between entrepreneurs and investors.

We consider it crucial that the backbone of a research cluster consists of major companies, as they offer the necessary track record and knowledge of successful commercialization. Even an internationally recognized research institute without an evident track record of commercialization would not offer significant enhancement to the present situation vis-á-vis investors, risk control and information asymmetry, whereas it could spur an outflow of innovations and human capital to companies abroad.

A Learn-and-Let-Go strategy as a tool for successful commercialization

The fully capitalized cost of developing a new drug, including studies conducted after the product receives regulatory approval, was estimated at 897 million dollars in 2003, and only 21.5% of drugs that begin Phase 1 human trials are eventually approved for release to the public, with only three out of ten launched products generating after-tax returns (DiMasi et al., 2003). These are overwhelming odds, even for an established biotechnology company. Within Finland it can seem even naive to have the goal of becoming a full-blown drug development company – that is, to be able to take a product from innovation to market. Nonetheless, some Finnish pharmaceutical companies have been able to bring new chemical entities (NECs) to market successfully.

Currently and in the near future Finnish biotechnology companies have to articulate a clear, viable strategy in order to be credible to the financial markets. Each of the following factors has been identified as an obstacle to the credibility of Finnish biotechnology companies or projects (Nikulainen et al., 2006, Hussi et al., 2006):

- Tendency to overemphasize the value of basic research despite an officially disclosed goal of commercialization
- Strong technology orientation
- Reluctance to share knowledge concerning innovations with investors and other evaluators
- Difficulty accepting skills from outside the sector; typically, the need for specific expertise and experience in the commercialization process is not acknowledged
- Reluctance to accept dilution of a minority position in the company
- Overestimation of managerial skills
- Tendency to tamper with set strategies

These issues are typical of high-technology and research-intensive sectors. Due to the limited domestic potential, close collaboration with larger players in these fields is a necessity; but the obstacles above impede cooperation.

A dynamic strategy is based on the idea of sequential learning: to develop a product within the company only when the skills required for its development match the core competencies of the firm. The next phase of development should be realized in collaboration with an experienced player in that field. The disclosure of a sequential learning strategy expresses to the market how the company can create value in the long run and hence maximize its present value of today.

A major challenge of a sequential learning strategy is that a dynamic flow of products places pressure on the company to perpetually evolve. The additional strain can at least partially be controlled by a structured, systematic approach to the execution of strategy, with knowledge and personnel management as critical issues.

Tacit knowledge accumulating through collaboration should be systematically converted into structural knowledge within the company, preparing the company to enter the next phase of development. However, when the product enters the next phase of development, the firm should out-license it and focus on the next product in the pipeline, developing that product one step further in-house based on the knowledge acquired from the previous collaboration. Personnel can be allowed to move with the out-licensed product to the collaborating company, thereby extending the network underlying potential collaboration.

The aim is to create a dynamic flow of products and, when deemed beneficial, of personnel, while building the company's structural knowledge. The sequential out-licensing of products results in an earlier flow of income and a better control of the risks inherent in biotechnological development. A concise strategy should also enhance credibility among investors and lead to better terms of outside financing.

Bioinformatics as a technology platform

The key to understanding the functions of cells and biological systems lies in a better understanding of their genetics. With the development of high throughput sequencing equipment, the collection of data has expanded exponentially. Bioinformatics has developed specifically to extract knowledge from massive databases (Muilu et al., 2007).

The basic principles and challenges for data refinement are strikingly similar across all fields of biotechnology.We conclude that bioinformatics could serve as a successful technology platform for the entire Finnish biotechnology industry.

Bioinformatics, in its broad definition, is the backbone of the value creation path: sequence analysis, genome annotation, gene and protein expression analysis, structure prediction, and biological system modeling range from core DNA to the complex cellular subsystems (Eskola, 2005; Bioinformatics Organization, 2009; EBI, 2009; NCBI, 2009). Finland clearly has a strong IT industry, and there are several research groups and companies that have been able to build significant knowledge in the field of bioinformatics, spurred by top-notch gene research, which requires effective and efficient computational skills.

The bioinformatics companies gain from being able to sell not only top-notch processing ability, but also to offer results based on proprietary data; this can result

in an absolute competitive advantage. The companies can create high-value but well-protected data-processing tools in close co-operation with the National Institue for Health and Welfare and research teams, offering excellent R&D potential. Additionally, the potential is created for a dynamic flow of people from research teams to bioinformatics companies, as well as for a possible exit of bioinformatics professionals to companies that utilize the data analyzed.

Can Finland attract large pharmaceutical companies?

Biobanks have been regarded as a crucial source for new data and novel approaches on the way to more effective drug development and personalized medicine – especially if the biobanks are combined with longitudinal patient data banks (Kingsmore et al., 2008; Schrattenholz and Soskic, 2008; Lum et al., 2009). Finland has strong Finnish epidemiological cohorts including more than 120,000 persons with DNA and serum samples as well as follow-up data and serum samples from 700,000 mothers since year 1983. Moreover, case Finland offers the combination of

- a genetically homogenous population
- an enrichment of rare diseases
- population records since 1634
- reliable health care registers of a one payer health care system
- genetic predisposition of certain common diseases in Finland,
- "inbred" training of clinicians
- favourable attitudes by public
- high degree of environmental homogeneity
- internationally recognized genetic research
- high quality epidemiology and mathematics
- top expertise in information technology

that together are considered to form an attractive combination for both top scientists as well as drug development companies (Peltonen, 2004; Eskola, 2005; Eskola, 2008; Vuorio, 2008).

The government view

It is in the best interests of Finland to use the aforementioned data banks and to protect them from exploitation in an unrefined, low-value form. The greatest amount of value would be captured by processing the data as far as possible domestically. Processing the data banks domestically protects the data, as only the results of

the data-mining are delivered to the customers. The valuable raw data, as well as the valuable information-processing data, remain the property of domestic entities. Through such an arrangement the respective research institutes, universities, hospitals, and the present main proprietor of the patient data banks, the National Institue for Health and Welfare, can refine their data and thus create value in the form of (1) more valuable end-products and (2) spillover data that can be utilized for further Finnish research.

For the National Institue for Health and Welfare, thoughtful, well-controlled utilization of the data banks would maximize value creation by accumulating new, useful data based on the mining of existing data banks. The National Institue for Health and Welfare can guide the utilization of the patient data banks emphasizing positive national health outcomes.

For society, a biotechnology cluster such as the one we propose would steer support to domains aligned with improving national health, with the ultimate goal of promoting the well-being of citizens and controlling the growth of health care costs. In the long term, the cluster would also be a natural way to increase partnerships between multinational pharmaceutical companies and domestic firms for projects that are in Finland's interests.

Finally, governmentally controlled patient data bases and patent pools can offer an increased total value for both society and business as opposed to a scattered set of individual intellectual property rights (IPR). The usage of an IPR pool is important in order to prevent the creation of an so called anti-common, where an individual IPR forms a gridlock in the value chain of developing a new technology (Heller and Eisenberg, 1998; Heller, 2008). The IPR owner can be tempted to exploit the entire value of a venture despite their property being a crucial but small sub-section of the value chain (Vanneste et al., 2006). This can lead to an underuse of innovations and thereby lost opportunities.

Our clusters can also be viewed as a proposal for a governmentally subsidized program. At the current developmental stage of the biotechnology industry the "technology programs" should become clearly focused on [distinctive] application areas rather than on an individual technology or bundle of technologies. This would guide companies to focus on customer needs earlier, at the initial phase of the project.

9.4.4 Policy recommendations

The above examples could be seen as a potential pathway to success in a small open economy. In both examples the government has an active role in promoting new policies and mechanisms to support locally anchored but international top-notch research and development. Tekes, the Finnish Funding Agency for Technology and Innovation has recognized the need for a nation-wide mechanism to promote the future success of local innovation. This has resulted in a decision to establish six Strategic Centers for Science, Technology and Innovation.

The Strategic centers for science, technology and innovation are aimed at offering top research institutes and companies a new way of carrying out close, long-term cooperation. In the strategic centers, companies, universities and research institutes will agree on a joint research plan aiming at practical applications by companies within a five to ten year period. International cooperation is defined to play a key role in the operation of the centers. In addition to shareholders, public funding organisations will commit themselves to providing funding for the centers in the long term; a significant part of future R&D support will be directed through these Strategic Centers for Science, Technology and Innovation.

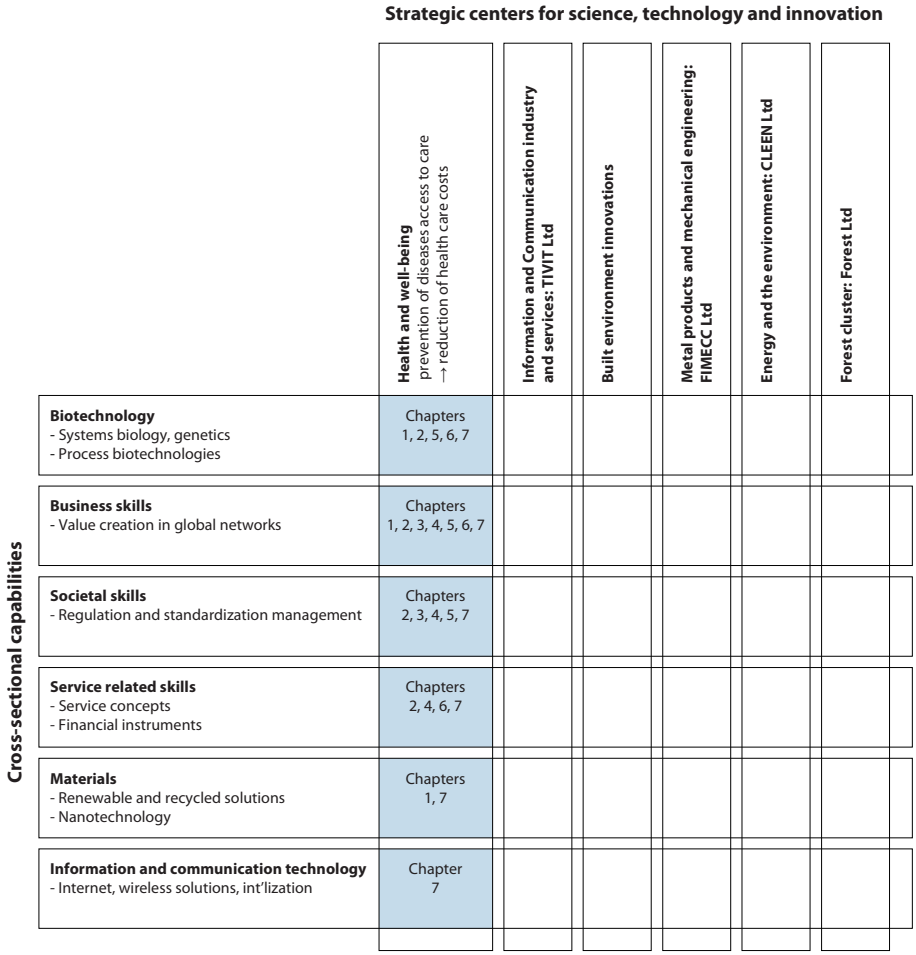
A Strategic Center for Health and Welfare was launched in April 2009. Figure 9.5. presents identified cross-sectional capacities within the Strategic Centers for Science, Technology and Innovation as presented in Tekes' 2008 innovation strategy, with a special emphasis on the new Health and Welfare Center as related to issues described in the chapters of this book.

If the pharmaceutical and biomaterial clusters above aimed to be strengthened, the giants should clearly see transparent incentives and reasons to locate significant volume of R&D activity in Finland. This might be possible and fruitful as a part of the Strategic Center for Science, Technology and Innovation for Health and Welfare. We suggest the formation of a development support center organized as a foundation or non-profit company owned by the pharmaceutical and health care industry and a government actor.

Our concern is that Finland, as any other small open economy, has attempted to construct a domestic biotechnology clusters for decades without any breakthrough. Having been said that, we see an intensive collaboration with international pharmaceutical giants as the only realistic option. The collaboration could advance in a following manner:

1. International pharmaceutical companies (together with players in the Finnish health care system) invest in the Center for Health and Welfare so that the Center can run 5-10 years.

Figure 9.5 Strategic centers for Science, Technology and Innovation strengthened by cross-sectional capabilities chosen in Tekes' innovation strategy (2008). Chapters of this book are shown in cross-sections of the centers and capabilities.



2. The Center for Health and Welfare utilizes Finnish databases and capabilities and conducts research in collaboration with the companies.
3. The Research and development projects between Center for Health and Welfare and the companies are funded by the EU, Academy of Finland and Tekes.

4. The Center for Health and Welfare would have a licence to analyze even highly classified data and provide researchprovide research results for specified purposes agreed with the companies involved in the projects.
5. Companies utilize the analytical results in their research and development activities. Results for any other purposes are ordered from the center distinctively.

This is in line with the national innovation strategy published by the ministry of employment and the economy. The strategy states:

> "Finnish innovation activities should be reinforced by a number of means, such as reinforcing international operations, increased involvement of users and customers in innovation processes, and broader approach to creativity and innovation.
>
> ...
>
> The development of a broad-based innovation policy will be built on our strong competence base and research system. If Finland desires to be a leading country in terms of research, technology and innovation, we must augment our investments in research and technology with a new demand- and user-oriented innovation policies."

This kind of wide collaboration base will benefit all parties and the Finnish cluster will become a vital part of the global value network. And, the Center for Health and Welfare with the wide financial basis will provide a balancing act between government regulation and prosperous medical innovation.

9.5 Conclusion

In many countries, significant government effort has gone toward creating a strong biotechnology industry base. However, the infrastructure developed so far has not yet met expectations in most cases. Government policies are inherently controversial, as they simultaneously facilitate and regulate the business. This book analyses the impact of government interventions in the biotechnology business and innovation system.

In healthcare, the large number of stakeholders generates a great degree of complexity. All stakeholders have to be taken into account in any business strategy and government intervention. This book presents a strategic framework to provide a solid basis for analysis and planning of innovation policy and business activity in a small open economy before deciding a new direction of policies. The framework could also be used as a tool considering the opportunities and threats of any country or region in the context of the regional division of labor.

The findings in this book can be extended to be used in other application areas related to biotechnologies. For instance, biotechnology-based applications provide energy efficient solutions. These solutions are showing far-reaching economic impacts on all industrial activity. Any prospective technological leap could facilitate implementing these economic impacts proactively in issues that have been identified as crucial for sustainability but beyond technological reach. For instance, health promotion and preventive products and services have been a core issue in health strategies for decades. To date, biotechnology applications such as functional food and personalized medicine seem to finally help to reach these distant goals.

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