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LOOKING OVER THE SHOULDERS OF GIANTS

A study of the geography of big pharma R&D and manufacturing operations

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Title: Looking over the Shoulders of Giants - A study of the geography of big pharma R&D and manufacturing operations
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ABSTRACT: Despite the fact that the reasoning behind location of large pharmaceutical firms is largely known, the exact geographical configuration of their activities is largely unknown. The aim of this master's thesis is to identify this unknown geographical configuration of big pharma R&D and manufacturing units. By analysing this empirical data, areas of high concentrations of big pharma activity and trends in localisations can be identified. Following this, analyses from different perspectives have been carried out to explain certain aspects of these localisations and trends. In order to achieve this, a database of the units was constructed. Information was based primarily on corporate information sources and secondarily on other sources such as online newspapers and industry studies. The study was limited to include only R&D and manufacturing units relating to human pharmaceuticals. The identification and mapping of big pharma operations indicates areas with high density of big pharma operations, or clusters. In brief, R&D units and manufacturing operations are concentrated in Western Europe, North America, and Asian countries such as China, Japan, India, and Singapore. Furthermore, a shift towards Asia, especially Singapore, China and India, in big pharma localisation can be observed. In general, the location of R&D units is driven by access to scientific competence; this is confirmed by an analysis relating the location of R&D in Europe to the location of biotechnological strongholds. Manufacturing seem to be driven to a greater extent than R&D by cost optimisation, such as taxes, labour costs, and economic incentives.
Keywords: big pharma, biotech, localisation, cluster, manufacturing, R&D, Vinnova, pharmaceutical industry, geographical mapping

About VINNOVA

VINNOVA - Swedish Governmental Agency for Innovation Systems.

VINNOVA´s mission is to *promote sustainable growth*
by funding *needs-driven research*
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Through its activities in this field, VINNOVA aims to make a significant contribution to Sweden´s development into a leading centre of economic growth.

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Research and Innovation for Sustainable Growth

Looking over the Shoulders of Giants

A study of the geography of big pharma R&D and manufacturing operations

by

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Nancy Özbek - Karolinska Institutet

Preface

In December 2006, VINNOVA was assigned by the Swedish Government to carry out an international study to shed light on the competitiveness of the Swedish sectorial innovation systems of pharmaceuticals, biotechnology and medical technology in international comparison.

The study includes analyses of three main focus areas from an innovation system perspective:

- Key players in the Swedish innovation system, who they are and their position in an international comparison
- Trends, initiatives and commitments in other countries/regions
- Comparative case studies to investigate the competitiveness of the Swedish innovation system

The main question is what structure, growth and development capacity does the Swedish pharmaceuticals, biotechnology and medical technology industry have compared to other countries/regions excelling in this field?

The present master's thesis is one of the studies carried out as part of the project. The aim is to identify the unknown geographical distribution of big pharma R&D and manufacturing units. Areas with high concentrations of big pharma activity and localisation trends are identified by an analysis of the empirical data. Analyses from different perspectives are then carried out to explain certain aspects of these localisations and trends.

The project manager of the government commission is Anna Sandström at the Strategy Development Division of VINNOVA. The authors of the present master's thesis are Johan Lindman, Industrial Engineering, Royal Institute of Technology; Jonas Timsjö, Sociotechnical Systems Engineering, Uppsala University and Nancy Özbek, Medical Science and Biomedicine major, Karolinska Institutet.

VINNOVA in November 2008

Göran Marklund
Director and Head, Strategy Development Division

Acknowledgement

This master's thesis is a Bio-Entrepreneurship-Team-project (BET-project) written for Vinnova, the Swedish Governmental Agency for Innovation Systems, and UBE – the Unit for Bioentrepreneurship at Karolinska Institutet in Stockholm, Sweden. BET-projects bring students of different educational backgrounds together in projects such as this.

Since this master's thesis will be examined at three different universities there is a need to distinguish the individual parts from each other. This will be clarified in section 1.3.1.

We would like to take this opportunity to extend our grateful thanks to everyone who in one way or another has participated in the process of this master's thesis.

In particular, we would like to thank Anna Sandström, supervisor at Vinnova, and Bo Norrman, supervisor at UBE, for allowing us to write this thesis, for help and feedback along the way and for general support during the process. The completion of this thesis would not have been possible otherwise.

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Stockholm, 10th January, 2008.

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For further information on Vinnova visit www.vinnova.se
For further information on UBE visit www.lime.ki.se/ube
For further information on BET-projects visit www.lime.ki.se/ube_courses2

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Abbreviations

A*STAR	*Agency for Science, Technology and Research, Singapore*
CHF	*Swiss Franc*
DBF	*Dedicated Biotechnology Firms*
EDB	*Economic Development Board, Singapore*
EEA	*European Economic Area, EU-27 plus Norway, Iceland and Liechtenstein*
FDA	*Food and Drug Administration, USA*
FDHA	*Federal Department of Home Affairs, Switzerland*
FDI	*Foreign Direct Investment*
FY	*Fiscal Year*
GNP	*Gross National Product*
HEA	*Higher Education Authority, Ireland*
HHS	*Department of Health and Human Services, USA*
IDA	*Industrial Development Authority, Ireland*
ICT	*Information and Communication Technology*
ILP	*Industrial Liaison Program, MIT, USA*
ILO	*(1) Industrial Liaison Office, Singapore* *(2) Industrial Liaison Officer, MIT, USA*
IVCA	*Irish Venture Capital Association*
MIT	*Massachusetts Institute of Technology*
MNC	*Multinational Corporation*
NDP	*National Development Plan, Ireland*
NIH	*National Institute of Health, USA*
NPPA	*National Pharma Pricing Authority, India*
NUS	*National University of Singapore*
OECD	*Organisation for Economic Cooperation and Development*
OTD	*Office of Technology Development, Harvard, USA*
R&D	*Research and Development*
SFI	*Science Foundation Ireland*
SBIR	*Small Business Innovation Research, USA*
SSF	*Single Sales Factor, USA*
STTR	*Small Business Technology Transfer Research, USA*
TNC	*Trans-national Corporation*
UCC	*University College Cork, Ireland*

1 Introduction

It is well-known that life science and its related industry sectors comprise up to one sixth of GNP in advanced economies[1]. A significant proportion of this industry consists of activities relating to research, production and marketing of pharmaceuticals. The global pharmaceutical market had an estimated value of USD 640 billion in 2006[2], with the 10 largest companies making up 40% of these revenues[3].

Due to the size of the industry, it is not surprising that some of the largest pharmaceutical companies are among the largest corporations overall. Indeed, a fair share of them such as Pfizer, Johnson&Johnson and Sanofi Aventis qualify for the Fortune Global 500. Typically these multinational corporations (MNCs) are involved at all stages of pharmaceutical R&D, production and sales. Ultimately profits are generated by the discovery of successful drugs. Thus, the main asset for these large pharmaceutical firms is their knowledge base. The industry has become increasingly knowledge-intensive following scientific advances in genetics and molecular biology. This has helped explain many of the previous unknown mechanisms of drugs. Indeed, ever-increasing investments are being put into R&D so as to ensure the *pipeline*[4] is full of drugs.

Moreover, the pharmaceutical industry is *ultra-slow* in comparison to other high-tech industries; on average, it takes 8 to 12 years from discovery of a cure to when a finished drug goes on the market[5]. Thus, the current profits of companies are usually the result of scientific findings a decade ago.

There are several accounts (academic[6], governmental/policy[7] and commercial[8]) as to how these MNCs reason when establishing new operations. Most of these reports focus on the location of R&D and manufacturing operations. The location of R&D operations is usually governed by factors relating to the availability of skilled scientists,

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[1] Cooke, 2005, pp. 325-341.
[2] *The Pharmaceutical market*, 2007, http://www.vfa.de/en/statistics/pharmaceuticalmarket/.
[3] Rosen, 2005, http://wistechnology.com/article.php?id=1903 .
[4] The drug-pipeline orders potential drugs according to their position in the development process. Stages include research/discovery, clinical research (stages I-IV) and post-market evaluation. (Source: http://www.phrma.org) .
[5] *Pharmaceutical Industry Profile,* 2006, http://www.phrma.org/files/2006%20Industry%20Profile.pdf .
[6] See for example Hanson (2004) and Cooke (2004b).
[7] See for example Eklund, Hallencreutz & Lindqvist (2007).
[8] See for example NERA (2007).

acclaimed research institutes and universities. The location of manufacturing facilities is governed by a combination of cost reduction factors (such as tax-levels) and factors that ensure quality (such as skilled personnel) depending on the regulatory requirements for the specific drug.

Despite the fact that the reasoning behind location of large pharmaceutical firms is known, the exact geographical configuration of their activities is largely *unknown*. The overarching purpose of this co-written master's thesis is dedicated to the identification, presentation and analysis of such a (global) geography.

1.1 Purpose and research question

The purpose of this co-written master's thesis is to *identify*, *present* and *analyse* the geographical configurations of big pharma R&D and manufacturing activities.

The essay owes its structure to the chronology (identification, presentation and analysis/discussion) intimated above. The *identification* of the geography of big pharma R&D and manufacturing activities can be broken down into two principal undertakings:

- What is the area of study? A satisfactory answer to such a question includes definitions of key concepts such as big pharma, manufacturing and R&D.
- How will this area of study be identified? To answer this question decisions have to be made as to what sources to address and how to evaluate the information collected.

Secondly the geographical concentrations of big pharma R&D and manufacturing activities will be *presented* at national and local levels as well as in regard to dynamics. The purpose of this section is to answer questions of the following nature:

- Where can large concentrations of big pharma R&D and manufacturing activity be found?
- Are there geographical areas with increasing or decreasing concentrations of manufacturing or R&D activity (in terms of recently established or closed facilities)?

Thirdly, the geography of big pharma of manufacturing and R&D activities will be *analysed* (and as far as possible explained). Naturally, this can be done in infinite number of ways depending on the theoretical framework chosen. Moreover the analysis is dependent upon the actual results and will draw attention to irregularities and patterns identified in this geography. Thus, our analysis includes an assessment of different *regions of interest (as*

suggested by our results), different *theoretical standpoints,* and a comparison with other *accounts in the literature*.

Based on these first research questions, further research questions and focuses for the individual analyses were identified:

- Does the corporate view of ideal localisations in the pharmaceutical industry differ from the reality?
- Can a correlation be seen between big pharma R&D and areas of biotechnological excellence?
- Benchmarking of four clusters with a major big pharma presence
- What are the determinants of national advantage (or disadvantage) for China and India?

1.2 Outline

Chapter 1, the current chapter, gives an introduction to the paper and states its purpose, research questions, delimitations, and definitions. This is followed by:

- *Chapter 2* which identifies and defines the field of the study.
- *Chapter 3* which briefly describes the pharmaceutical industry to give the reader a basic comprehension of it, the drug development process, the history, and some accounts on the future of the industry.
- *Chapter 4* explains the methodology used to determine the geography of big pharma R&D and manufacturing units.
- *Chapter 5* gives a summarised view of the empirical study on big pharma localisations, in figures and text.
- *Chapter 6* highlights some of the trends found in the collected empirical data.
- *Chapter 7* presents the general theoretical framework used, giving an overview of theories regarding location of manufacturing and R&D operations.
- *Chapter 8* conducts a comparison between the findings of the empirical study and an industry concept of the ideal pharmaceutical company.
- *Chapter 9* introduces a specific theoretical framework used to study the geography of big pharma R&D in Europe.
- *Chapter 10* gives an overview of the reasoning around localisation of the pharmaceutical industry, including examples from the empirical study.
- *Chapter 11* consists of a description and comparison of four leading biopharmaceutical clusters.
- *Chapter 12* analyses the observed shift towards Asia, by conducting a SWOT-analysis on China and India.

- *Chapter 13* consists of a discussion of the future of big pharma and the pharmaceutical industry. Furthermore there are some remarks on the methodology as well as suggestions for further studies.
- *Chapter 14* summarises accounts on the geography of big pharma R&D and manufacturing found in both the results and analysis.

1.2.1 Individual parts

To enable individual examination at the different universities grading this paper, the individually written parts need to be distinguished. For that reason, these parts have been marked with a symbol representing the author: Johan Lindman (λ), Jonas Timsjö (θ) and Nancy Özbek (Ω). Chapters without symbols have been co-written.

1. Introduction
2. Identification
3. Background
4. Method
5. Empirical Data
6. Trends in Big Pharma Localisation - λ
7. Location Theory
   7.1 - θ
   7.2 - 7.3- λ
   7.4 - Ω
   7.5 - λ
8. Localisation in the Pharmaceutical Industry - λ
9. The Ideal Company - λ
10. Big Pharma R&D in Europe - θ
11. Clusters - Ω
12. The Shift to Asia - λ
13. Discussion
14. Conclusion

Identification

This section identifies the field of this study; including delimitations, definitions and background information. This sets the study in context before the data is presented and analysed.

2 Identification

This study has been limited to studying big pharma, big pharmaceutical companies, as defined in the following section (1.3). Furthermore, the mapping has been focused on manufacturing and R&D units relating to human pharmaceuticals and vaccines. This is further developed in chapter 3, Method.

2.1 Definitions

Some definitions of importance to the rest of the paper will be given here.

2.1.1 Manufacturing and R&D operations

Manufacturing is defined as the process where pharmaceuticals are made. Likewise, a *manufacturing unit* is a structure that produces pharmaceuticals.

Research & Development (R&D) is a set of activities required to take a lead compound to commercial manufacturing of a finished drug. A unit conducting these operations is referred to as an *R&D unit*. An important note for this study is that no distinction between research and development is generally made, even though they differ from each other in reality. *Clinical trials* have not been included in this study. Similarly, production of pharmaceuticals exclusively for clinical trials has been excluded when listing manufacturing units.

2.1.2 Big pharma

There are a vast number of references to big pharma in the reviewed literature. These include sources such as scientific papers, industry reviews, newspapers and Internet blogs. Disappointingly few of these references adopt any clear-cut definition of this concept. Generally, however, these companies are characterised by their *business activity* (pharmaceuticals), their (large) *size* and the (great) extent of *vertical integration*. In this thesis, a definition of big pharma has been adopted to overlap these more conceptual big pharma characteristics often referred to in literature.

The business activity of these large pharmaceutical firms can be divided into different categories depending on the type of drugs being developed, produced and sold:

- Ethical or prescription drugs[9].
  (Drugs that (mostly) require prescription by a physician)
- Over-the-counter (OTC) medicines.
  (Drugs that can be bought without prescription)
- Veterinary pharmaceuticals.
  (Animal medicines)
- Generic drugs
  (Drugs that mimic pre-existent (ethical or OTC) drugs with patent expired)
- Vaccines
  (A substance with the potential to enforce immunity to certain disease)

Furthermore pharmaceuticals can be divided according to the type of molecule comprising the active pharmaceutical ingredient. Typically these fall into one of the following two broad categories:

- *Biopharmaceuticals* are larger biological structures such as proteins or nucleic acids.
- *Small molecular entities* (generally referred to as pharmaceuticals) are smaller molecular structures usually derived from chemical reactions and processes.

Most pharmaceuticals today are small molecular structures. Most biopharmaceuticals are ethical drugs because they have a more recent history and so are still protected by patents. When this paper references pharmaceuticals, it includes vaccines and biopharmaceuticals.

Our definition of big pharma includes the top 50 pharmaceutical companies in terms of annual revenues. The list used was compiled by Pharma Executive and is based on the sales of prescription drugs for the fiscal year 2005[10]. An important notice is that the revenues are only for the human pharmaceutical part of the businesses, revenues from other parts have been omitted. The companies included in the study are listed below.

[9] Ethical drug is a synonym for a prescription drug that is often favoured by pharmaceutical companies, despite being less widely understood. (Source: http://moneyterms.co.uk/ethical-prescription/).
[10] Gray, 2006, http://www.pharmexec.com/pharmexec/data/articlestandard//pharmexec/272006/354138/article.pdf .

Figure 1: Pharma Executive Top 50 pharmaceutical companies

The Pharm Exec 50

1 Pfizer	11 Abbott labs	21 Novo Nordisk	31 Altana	41 Watson
2 GlaxoSmith Kline	12 Roche	22 Eisai	32 Chugai	42 Biogen Idec
3 Sanofi Aventis	13 Amgen	23 Teva	33 Solvay	43 Shire
4 Novartis	14 Boehringer-Ingelheim	24 Merck KGAA	34 UCB	44 Shionogi Seiyaku
5 AstraZeneca	15 Takeda	25 Sankyo	35 Genzyme	45 King
6 Johnson&Johnson	16 Astellas	26 Otsuka	36 Serono	46 Tanabe Seiyaku
7 Merck	17 Schering-Plough	27 Forest Labs	37 Allergan	47 Kyowa Hakko
8 Wyeth	18 Bayer	28 Daiichi	38 Mitsubishi	48 Mylan Labs
9 Bristol-Myers Squibb	19 Schering AG	29 Baxter	39 Gilead Science	49 MedImmune
10 Eli Lilly	20 Genentech	30 Akzo Nobel	40 Lundbeck	50 Ono

Source:http://www.pharmexec.com/pharmexec/data/articlestandard//pharmexec/272006/354138/article.pdf.

After compilation of the list, a number of changes have taken place, mainly due to mergers and acquisitions. These mergers and acquisition were within the list but mostly consisted of acquisitions of smaller companies. Examples include the merger of Bayer and Schering AG, AstraZeneca's acquisition of MedImmune and the merger of the Japanese companies Daiichi and Sankyo.

The companies included on this list all fulfil (or come close to fulfilling) the only clear-cut definition of big pharma found in the literary review[11]:

1 Sales of USD 2 billion a year
This is accomplished by the 37 top companies on the list, with the entire list having annual revenues above USD 1.2 billion.

2 International Operations
Including the sales operation, all the companies on the list have a clear international presence. However, a number of the smaller companies on the list have a clear national focus on their manufacturing and R&D operations.

3 Research and development of drugs in several therapeutic areas
The companies on the list are active in several therapeutic areas, even though many of them have a clear focus on one or two areas.

4 Fully integrated companies
All of the companies on the list are fully integrated pharmaceutical companies.

The reason for not following this definition strictly is that the concept of big pharma is used very differently in literature. However, in our literary review, criteria 2, 3 and 4 captures the essence of big pharma satisfactorily. Indeed, the 50 companies chosen fulfil these criteria. Rather, criterion 1 (annual sales of USD 2 billion) should be seen as an indicator of the probability of fulfilling the other three criteria if no information other than sales is assessed. Furthermore, the advantage of a generous definition

[11] Rosen, 2005, http://wistechnology.com/article.php?id=1903 .

including as many as 50 companies is that different subsets of the data can be explored and provide a larger sample upon which to base the analysis.

Both traditional and biotechnological pharmaceutical companies are included on the list. The biotechnological pharmaceutical companies included are usually referred to as big biotech. These companies share a common history in the sense that most of them were founded in the 70s and 80s as spin-offs from biotech universities (mostly in the US) and solely produce biopharmaceuticals. Traditional big pharma on the other hand are older companies producing pharmaceuticals derived from both biotechnological and chemical applications. However, for the sake of this study there is no need to distinguish between these companies and the other big pharma because in many other respects they are similar; for example, they all fulfil the definition stated above.

In the rest of this paper, the terms big pharma or top 50 pharmaceutical companies are used to refer to the 50 companies on the above list.

3 Background

In this section the main characteristics of the pharmaceutical industry will be outlined.

3.1 The pharmaceutical industry

The life science industry can be divided in to a number of areas: drug development and manufacturing, medical devices, and the medicinal, environmental, nutritional, and agricultural applications of biotechnology. The scope of this paper includes R&D, manufacturing, and pharmaceutical applications of biotechnology. These activities are commonly referred to as the pharmaceutical industry.

The size of the pharmaceutical market was estimated at USD 640 billion (2006), with the largest markets of the US and Europe making up 45% and 30% respectively[12]. The market as a whole has grown over 7% the last two years, and is expected to continue growing by 5-8% for the coming five year period. A number of emerging markets are growing at an even faster pace (showing double digit growth), for example China, Korea, Mexico, Russia and Turkey.[13]

Characteristic of the industry is a marked focus on R&D followed by major R&D expenditure. For example, looking at the top ten companies in terms of revenues, average R&D expenditure as a percentage of revenues was 23.8% in 2005[14]. One aspect of this is the fact that the cost of drug development gets higher as a drug nears completion; this gives rise to a situation where only the large companies have the necessary capital for this process. This is forcing smaller companies to sell their discoveries, or develop them as joint ventures.

3.2 Companies within the pharmaceutical industry

Traditionally, the pharmaceutical industry is divided into three groups according to the size of the company. The majority of the industry is made up of small and usually young companies, not infrequently originating from a research group. In general, these companies are focused on research and their manufacturing, sales and marketing capabilities are limited.

[12] *The Pharmaceutical Market*, 2007, http://www.vfa.de/en/statistics/pharmaceuticalmarket/
[13] Chu, 2006, http://www.drugresearcher.com/news/ng.asp?n=66620-ims-byetta-gardasil .
[14] 'R&D Expense Level in Leading Pharma Companies 2005', 2005.

The second category is the medium-sized firms, comprising some 200-300 companies. The companies within this group have evolved further from the first group, having established larger operational capabilities, such as manufacturing, sales and marketing. Many would argue that the first two groups are responsible for the majority of innovation in the industry[15].

The third category is commonly referred to as *big pharma*. These are multinational and integrated companies taking drugs all the way from a lead compound to a finished drug and continuing along the value chain manufacturing, marketing, and selling the drug.

This study only covers big pharma; but the real dynamics within the industry may well lie outside this group in the small and medium-sized companies, which fall outside our scope. Big pharma are coming from the outside, whereas the smaller companies generally grow from within a region.

3.3 Drug development process

Discovering and producing one new drug costs pharmaceutical companies about USD 900 million and its development takes on average 8-12 years. New medicines are developed as follows[16]:

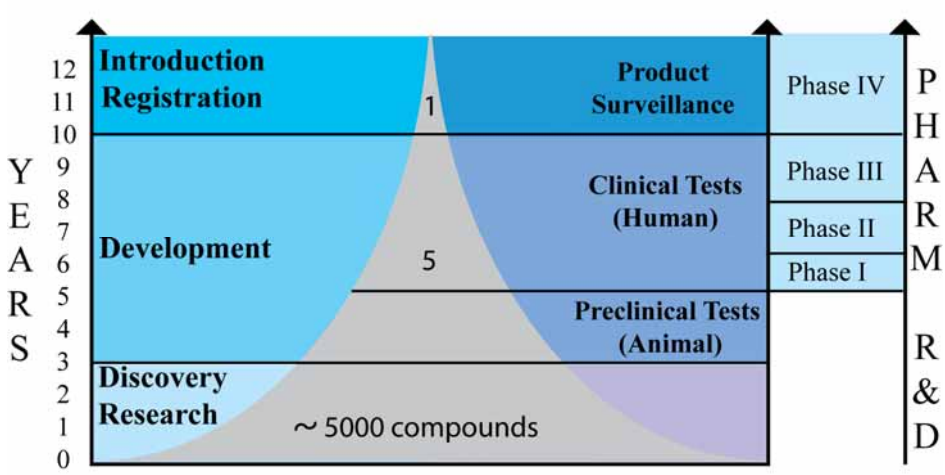
1 Discovery research: the development of a drug begins in a laboratory with chemists and scientists searching for chemical substances that target factors that play a role in diseases. Approximately, over 5,000 new substances are identified during this discovery research and only five of these are approved for further process in developing new medicine.
2 Preclinical testing: at this stage, the investigational drug must be tested outside the laboratory to ensure its safety. A pharmaceutical company conducts laboratory and animal studies to investigate the drug compounds' efficacy against the targeted disease. This testing usually takes from one to five years.
3 After preclinical testing, results of all testing must be provided to the FDA in the US or other regulatory agencies, to begin clinical testing on humans.
4 Clinical testing consists of phases I-IV. Phase I tests involve healthy volunteers to verify safety by studying how the drug is absorbed, distributed, metabolised, and excreted. Phase II involves volunteer patients (people with the disease) to determine efficacy and further study the safety of the candidate drug. Phase III involves a larger group of

[15] Laestadius, 2007, [Personal communication].
[16] *Pharmaceutical Industry Profile 2006*, 2006, http://www.phrma.org/files/2006%20Industry%20Profile.pdf .

patients in clinics and hospitals to test the efficacy and safety of the drug, usually in randomised, blinded clinical trials.

5 After phase III, the FDA or other regulatory agencies have to approve the New Drug Application (NDA). This includes data and files that the company has gathered containing all scientific information and analyses. After approving the NDA, the new medicine becomes available to prescribe, but for some medicines, the FDA requires additional studies, in other words phase IV. Phase IV studies expand the testing to a broader patient population and compare the long-term effects[17].

Figure 2: Drug development process



Source: http://www.phrma.org/files/2006%20Industry%20Profile.pdf

3.4 History

3.4.1 The early years

Many of the major pharmaceutical companies can trace their origins back to the chemical industry. Building on their chemical know-how, these companies expanded into pharmaceuticals. In many cases, their pharmaceutical branch was later moved into a subsidiary or independent company. Looking at the companies included in this study, a correlation can be found between the starting year and the rank on the revenue top list; the older companies are generally placed higher on the list, i.e. they have higher revenues. For the studied companies, the average founding year was 1906 and the median founding year was 1913.

However, since the early years a lot has changed in the dynamics of the industry. The pharmaceutical companies are generally more specialised in pharmaceuticals, and are less active in other business areas. During the early

[17] Ibid.

20th Century two major discoveries were made that had a huge impact on the industry, penicillin in the 1920s and insulin in the 1930s.[18]

3.4.2 World War I and II

The World Wars had significant effects on the pharmaceutical industry in several ways. Firstly, a number of German enterprises had their assets in the US seized under the *Trading with the Enemy Act*[19]. Examples of this included companies like Merck, formed from the US branch of Merck KGaA[20], and Schering-Plough[21], originating in the US branch of Schering AG (now Bayer-Schering pharma). Secondly, significant parts of production plants and laboratories were destroyed during the wars (especially during World War II), mainly in Germany and Japan. Thirdly, these wars created a high demand for medical treatment and pharmaceuticals thus also creating greater incentives to find new and more effective drugs.

3.4.3 Consolidation

The pharmaceutical industry is highly consolidated as a result of the large number of mergers and acquisitions over the years. Indeed, the top 10 companies in terms of revenue represent over 40% of the total industry revenues[22]. However, this consolidation has provided other opportunities. When companies have merged or been acquired industrial property is usually sold, creating an opportunity for small actors to launch generic or contract manufacturing. A second aspect is that major companies' are generally disinterested in drugs which generate smaller revenues (typically below USD 100 million annually). These drugs could then be bought by smaller more specialised companies.[23]

3.4.4 Generics

Generic manufacturing has grown into a major competitor for the big pharmaceutical companies, as they are able to provide the same drug at a lower cost due to much lower research expenditures and a specialisation on manufacturing. These companies are growing quickly at present; an example being the aggressively growing generics manufacturer Teva and

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[18] *Pharmaceutical industry*, 2007, http://www.britannica.com/eb/article-260305.
[19] An act giving the president, as an advocate of the state, the right to seize property of an enemy power. United States Federal Law. "Trading With the Enemy Act" 6th October 1917. (Source: http://www.treas.gov/offices/enforcement/ofac/legal/statutes/twea.pdf) .
[20] *History of Merck KGaA – Milestones 1919 to 1945*, 2007, http://www.merck.de/servlet/PB/menu/1328740/index.html .
[21] *History of Schering-Plough*, http://www.schering-plough.com/schering_plough/about/history_sp.jsp .
[22] Rosen, 2005, http://wistechnology.com/article.php?id=1903 .
[23] Rosen, 2007, http://wistechnology.com/article.php?id=3694 .

also Sandoz, a division of Novartis. Countries such as China with weaker intellectual property protection also have a thriving generics market.[24]

3.4.5 The rise of biotechnology

In the 1970s and 1980s the first major biopharmaceutical companies were founded by pioneers such as Amgen and Genentech. These companies often sprang out of research groups. During the 1980s, many them were struggling which forced them to partner with major pharmaceutical companies in order to survive. A great many of the smaller companies have been acquired to enhance the pipelines of larger pharmaceutical companies.[25]

The biotechnological development has given opportunities for a more rational drug discovery process. This has made the process more focused and less coincidental.

An upcoming opportunity is biogenerics - generics of biological drugs. These are more complex to manufacture, but India is investing majorly in order to be able to capitalise on such drugs when the patent of some major biopharmaceuticals expire[26].

3.4.6 The future

What the future holds for the pharmaceutical industry in general and big pharma more specifically is unclear. Two major trends have been observed: industrial consolidation and a focus on core competencies and outsourcing of other activities. It can also be seen that big pharma lacks innovation momentum; pipelines are weaker and a lot of new drugs are being bought from smaller and more specialised players[27].

The reason for the drying pipelines is usually explained by the inability of big pharma to adjust to the new logic of the industry with ever-increasing biotechnological applications in the pharmaceutical R&D and manufacturing process. One such new application of biotechnology is pharmacogenomics[28] which may enable the development of *tailor-made* drugs, that is, pharmaceuticals tailored for the specific genome of the

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[24] *Generic Pharmaceutical Association*, http://www.gphaonline.org/.
[25] Piribo Ltd, 2005; Vettel, 2006.
[26] Sandström, 2007, [Personal communication].
[27] Barrett, Carey & Amdt, 2005, http://www.businessweek.com/magazine/content/05_02/b3915433.htm, Rosen, 2007, http://wistechnology.com/article.php?id=3694 .
[28] Pharmacogenomics examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all. (Source: http://www.ncbi.nlm.nih.gov/About/primer/pharm.html).

individual. Whether big pharma will be able to survive in its current form, as fully integrated pharmaceutical companies, is a matter of debate and will be discussed towards the end of this paper.[29]

[29] 'Pharmacogenomics to replace pharma's business model', 2005, http://www.drugresearcher.com/news/ng.asp?n=58360-pharmacogenomics-to-replace .

4 Method

This paper consists of a quantitative study of the geography of big pharma manufacturing and R&D units. A positivistic standpoint is taken, viewing reality as an objective phenomenon with a logic connection between cause and effect. Using this approach, knowledge of the world is based on empirical data and analysis of it. The approach of the first part of this paper is descriptive and explorative, trying to give a view of localisation of the studied companies.

Further research questions were identified based on the results of the initial empirical study and original research questions. These questions will lead to the second part of the paper in which certain aspects of the results from the initial study will be explored.

4.1 The empirical study

The study was conducted by compiling a database of the manufacturing and R&D units of big pharma as previously defined. A choice of which units to map was required for the study. Inherent in the question of localisation as proposed in this study is the longevity of the investment and the commitment to both the investment and the region. Thus, R&D and manufacturing units where chosen since they represent a larger investment and commitment to the region. For example, a sales office could be opened up quickly by renting some office space, and moved just as quickly while a factory or a research lab is a long-term commitment and more capital and human resource-intensive.

Furthermore, the study was limited to include only operations involved in research, development and manufacturing of human prescription pharmaceuticals, and exclude areas such as diagnostics, medical technology and veterinary medicines. However, factories host a range of manufacturing activities and research laboratories undertake numerous research studies. Thus, some of the products produced and research studies undertaken at these sites are not always dedicated solely to human prescription pharmaceuticals. The available information did not always allow us to make distinctions between plants producing only human prescription pharmaceuticals and facilities producing other type of products as well.

4.1.1 Parameters

In the study, a number of parameters have been explored for the individual units. In this case, the most obvious parameter in a study on localisations,

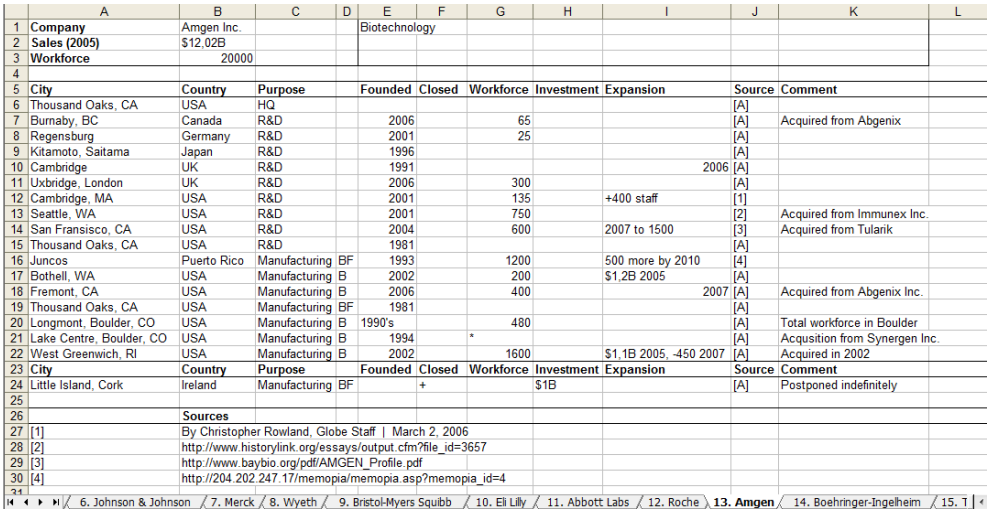
the geographical location, was represented by a city and a country. This parameter is necessary in order to conduct a geographical study. However, it can be argued that it should have been divided into entities other than countries or cities. Nevertheless in a study like this, working with close to 1,400 units on a global level, including new entities would complicate the data collection and cause too much additional labour.

To be able to unravel the dynamics of the localisation over a period of time, the founding and closing year (if applicable) of the units were included. For the sake of this study, the year when operations started was defined as the units' starting year. Likewise, the closing year was defined as the point in time when operations ceased. As far as possible, this is the year referred to in the study. However, this may vary in some cases depending on the sources used. Furthermore, an acquired unit is considered new, meaning that the year of acquisition is used in such cases and the same goes for a sold (closed) unit, where the year of sale is stated as a closing year. When a unit is sold between two companies included in the study, it will show up in the empirical data as one new unit and one closed unit.

The next parameters surveyed are the workforce, initial investment and any expansions conducted at the individual units. These three parameters were included to provide a measurement of the commitment to the localisation. This information was hard to find, and only available for a limited number of units. This is also viewed as additional information and is not within the core of the study.

In the database, the source of the information is also given in a rather general way, dividing the sources into three groups as explained in the next section. Comments were also added, most often referring to acquisitions of units or irregularities in the information. A screenshot of a sample page of the Excel database can be seen below, sorted by company. This example is from the database sheet for Amgen.

Figure 3: Database screenshot



	A	B	C	D	E	F	G	H	I	J	K	L
1	**Company**	Amgen Inc.			Biotechnology							
2	**Sales (2005)**	$12,02B										
3	**Workforce**	20000										
4												
5	**City**	**Country**	**Purpose**		**Founded**	**Closed**	**Workforce**	**Investment**	**Expansion**	**Source**	**Comment**	
6	Thousand Oaks, CA	USA	HQ							[A]		
7	Burnaby, BC	Canada	R&D		2006		65			[A]	Acquired from Abgenix	
8	Regensburg	Germany	R&D		2001		25			[A]		
9	Kitamoto, Saitama	Japan	R&D		1996					[A]		
10	Cambridge	UK	R&D		1991				2006	[A]		
11	Uxbridge, London	UK	R&D		2006		300			[A]		
12	Cambridge, MA	USA	R&D		2001		135		+400 staff	[1]		
13	Seattle, WA	USA	R&D		2001		750			[2]	Acquired from Immunex Inc.	
14	San Fransisco, CA	USA	R&D		2004		600		2007 to 1500	[3]	Acquired from Tularik	
15	Thousand Oaks, CA	USA	R&D		1981					[A]		
16	Juncos	Puerto Rico	Manufacturing	BF	1993		1200		500 more by 2010	[4]		
17	Bothell, WA	USA	Manufacturing	B	2002		200		$1,2B 2005	[A]		
18	Fremont, CA	USA	Manufacturing	B	2006		400		2007	[A]	Acquired from Abgenix Inc.	
19	Thousand Oaks, CA	USA	Manufacturing	BF	1981					[A]		
20	Longmont, Boulder, CO	USA	Manufacturing	B	1990's		480			[A]	Total workforce in Boulder	
21	Lake Centre, Boulder, CO	USA	Manufacturing	B	1994		*			[A]	Acqusition from Synergen Inc.	
22	West Greenwich, RI	USA	Manufacturing	B	2002		1600		$1,1B 2005, -450 2007	[A]	Acquired in 2002	
23	**City**	**Country**	**Purpose**		**Founded**	**Closed**	**Workforce**	**Investment**	**Expansion**	**Source**	**Comment**	
24	Little Island, Cork	Ireland	Manufacturing	BF		+		$1B		[A]	Postponed indefinitely	
25												
26		**Sources**										
27	[1]	By Christopher Rowland, Globe Staff | March 2, 2006										
28	[2]	http://www.historylink.org/essays/output.cfm?file_id=3657										
29	[3]	http://www.baybio.org/pdf/AMGEN_Profile.pdf										
30	[4]	http://204.202.247.17/memopia/memopia.asp?memopia_id=4										

6. Johnson & Johnson | 7. Merck | 8. Wyeth | 9. Bristol-Myers Squibb | 10. Eli Lilly | 11. Abbott Labs | 12. Roche | **13. Amgen** | 14. Boehringer-Ingelheim | 15. T

4.1.2 Sources

The data on which the empirical study is based was collected using sources that can be divided into three categories; material published by the company, direct communication with the companies and other sources. The material published by the company mainly consists of annual reports (including Form 20F), Form 10-K[30], corporate websites and press releases. The second category, direct communication with the companies, has mostly been conducted by email enquiries. The third category is more diverse, ranging from newspaper articles to market studies and scientific publications. The majority of the empirical study has been based on material published by the companies.

4.1.3 Method critique and evaluation

What needs to be kept in mind when gathering empirical data from corporate sources, is that the information provided is designed to promote that particular company. It is therefore not objective, although the information on most aspects of localisations seems to be accurate, for example when comparing with studies such as *Big pharma in Europe* by Björkman[31].

One aspect of the localisations causes more difficulties than the other when it comes to using corporate information; that of plant closure. During the study, it was observed that companies were reluctant to publish information

[30] Form 10-K is an annual report to the US Securities and Exchange Commission, giving an overview of the business activities and financial status of the enterprise.
[31] Björkman, 2007, [Personal Communication].

that can be interpreted as negative, such as closure of factories. However this information can be better assessed by using other more objective sources such as newspapers.

To assess the quality of data an evaluation was carried out based on the companies' own published totals for R&D and manufacturing units. Comparing this with the data collected in the empirical study established a measure of *coverage* of our data. However, this should not be seen as a definitive number so much as an indication that the geographical overview of big pharma based on the study is relevant. Coverage in this case was calculated by dividing the number of units found with the number of total units as stated by the company. After that, a weighted average was calculated. According to this average, the coverage of the empirical study was 97.8%. Furthermore, an evaluation was made in regard to the founding year of the units, the data on which the trend analysis is based. This evaluation showed that the founding year covered 71.2% of the units. A probable assumption is that the units with an unknown founding year generally started farther back in time and that newer units are better covered in this aspect.

Perhaps the largest flaw in this study is the fact that the volume or size of the units has not been satisfactorily established. This study has measured the number of units, rather than trying to establish their size in terms of, say, investment or staff. Conducting a geographical mapping based more largely on the size of the units is an area for further research and will be discussed more thoroughly in Chapter 11.

An alternative approach to the one taken in this study could have been to contact the companies directly, rather than searching their published information. Even though this approach might have given a more exact view, it is also much more time consuming. Furthermore, only a very limited number of people have an overall view of the localisation of these companies. Gathering information for the empirical study from the sources mentioned earlier was deemed most fitting for this paper.

Presentation

This section presents the empirical data collected for this study. The data is presented as figures, text and diagrams giving an overview of the localisation of big pharma. The presentation gives an overview rather than presenting all the data collected.

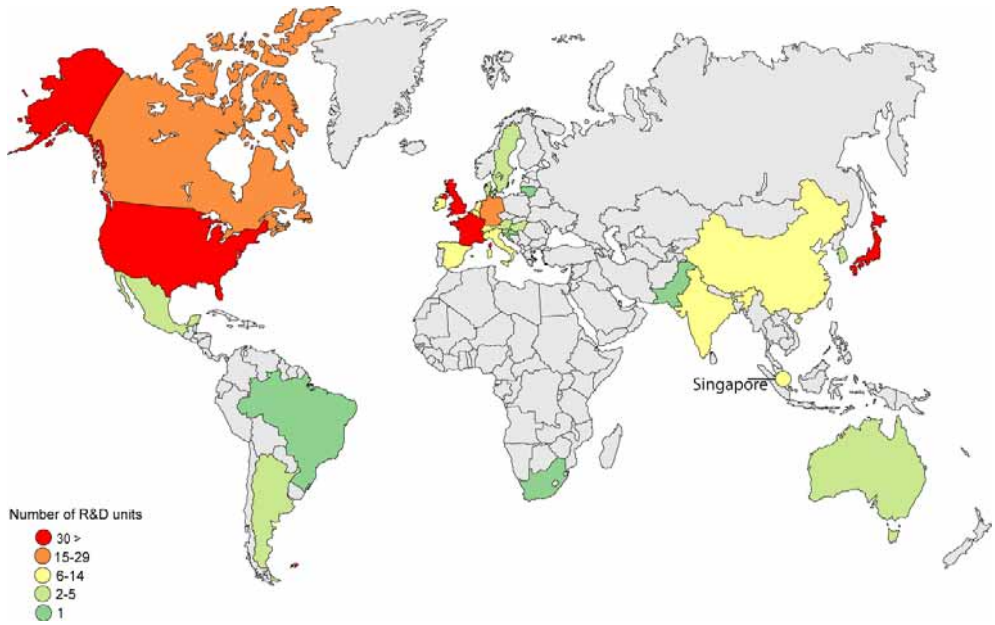
5 Empirical Data

This chapter will seek to provide an overview of the results of our empirical study of big pharma localisations. The results have been compiled in a number of figures and diagrams to give a general idea of the global distribution of R&D and manufacturing units. Unless otherwise state, all data in this chapter is gathered from the database containing the results of the empirical study.

Sorting the units by country is slightly problematic and, due to regional differences within countries, does not necessarily give a correct view of the localisation. For example, the units in the US are generally located in the states along the east or west coasts or in the Chicago area. Nevertheless, this method of visualising the localisations was chosen anyway so as to offer an overview of the big pharma presence. One reason for this is the difficulties of separating the units strictly by regions. However, maps showing clusterings or agglomerations have been created to give a more exact view of the worldwide distribution of units. These maps of agglomerations show the units gathered as clusters, sorted after geographical proximity. Units included in a cluster on the map lie within a circle of radius 50 kilometres.

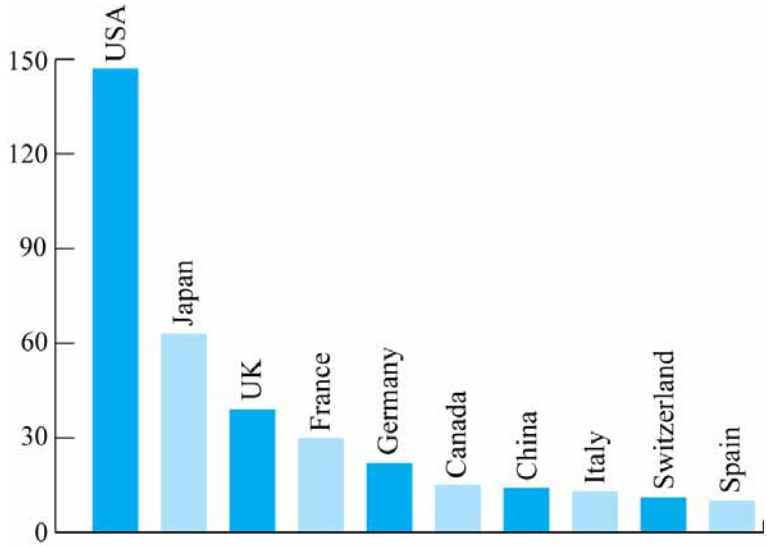
5.1 The geography of big pharma R&D

Figure 4: Concentration of R&D Units



As can be seen in figure 5, R&D operations are mainly concentrated in Western Europe, North America, and the four Asian countries Japan, China, India, and Singapore. In contrast to this, Africa, South America and the Middle East have a limited big pharma R&D presence. The countries in red display a huge difference in terms of number of units. For example, the US actually has nearly five times as many R&D units as France. The numbers are shown in greater detail in the diagram below, where it can be seen that the US has by far the most R&D units (147), followed by Japan (63), the United Kingdom (39), France (30), and Germany (22).

Figure 5: Top countries ranked by number of R&D Units

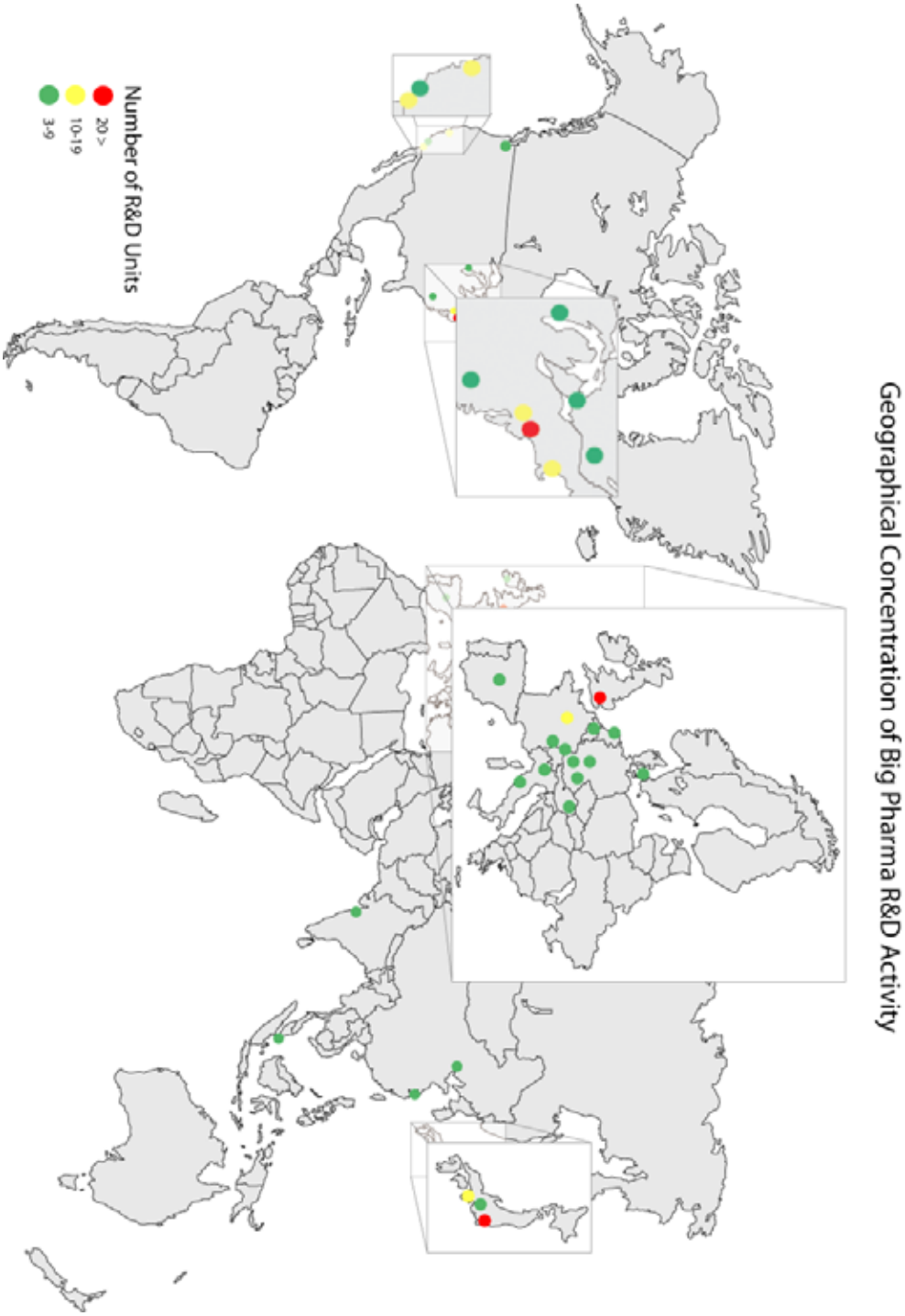


5.1.1 R&D agglomerations

The cluster map in figure 7 has been created from the data collected in regard to localisations of R&D. It can be seen that the densest clusters are close to the large cities New York (New Jersey), London and Tokyo. Furthermore, a clear concentration can be seen near the coasts of the US, in Western Europe and in Japan. Important areas here include the Boston/Cambridge area (Massachusetts), the Californian cities of San Diego, San Francisco and to some extent Los Angeles, plus Paris and Osaka.

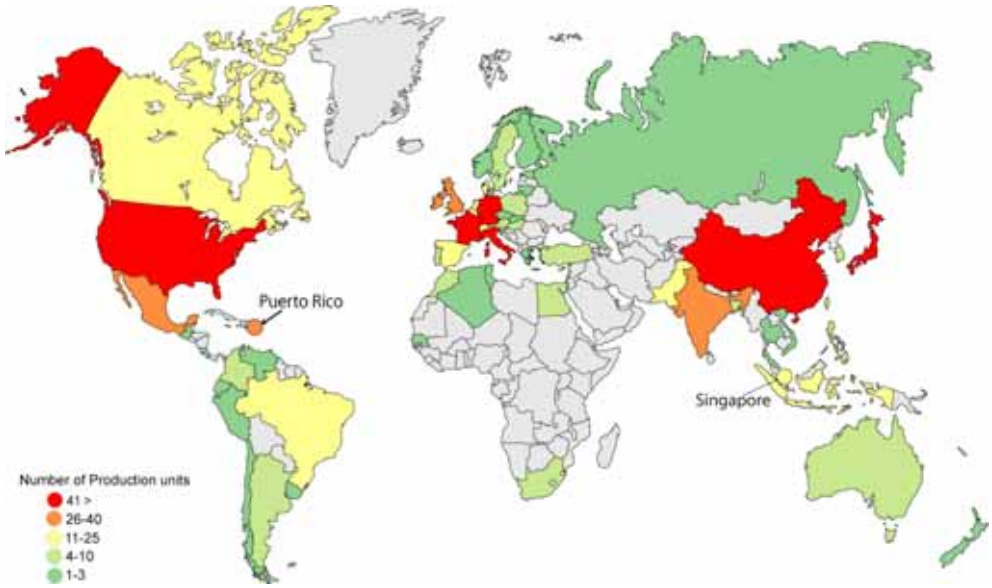
Please note that in the following map, which enlarges certain areas, no clusters are hidden behind the enlargement. The same also applies to the cluster map of manufacturing units.

Figure 6: Concentration of R&D Units shown as clusters



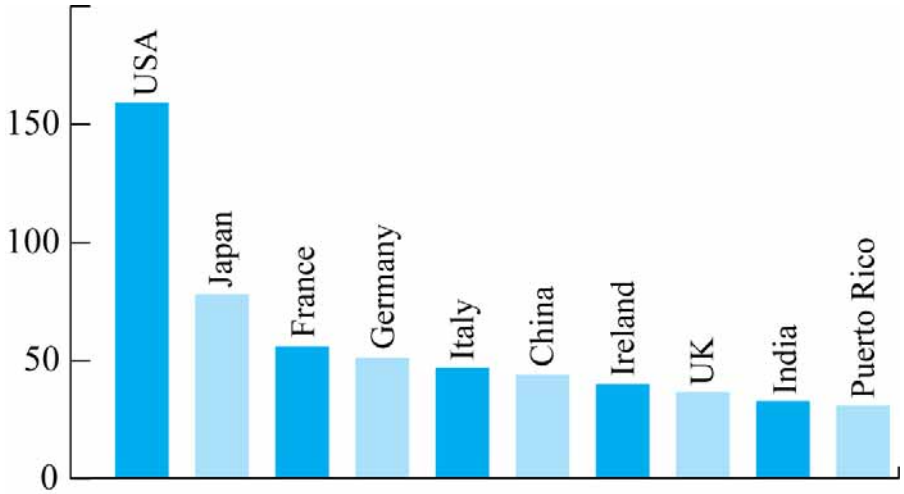
5.2 The geography of big pharma manufacturing

Figure 7: Concentration of Manufacturing Units



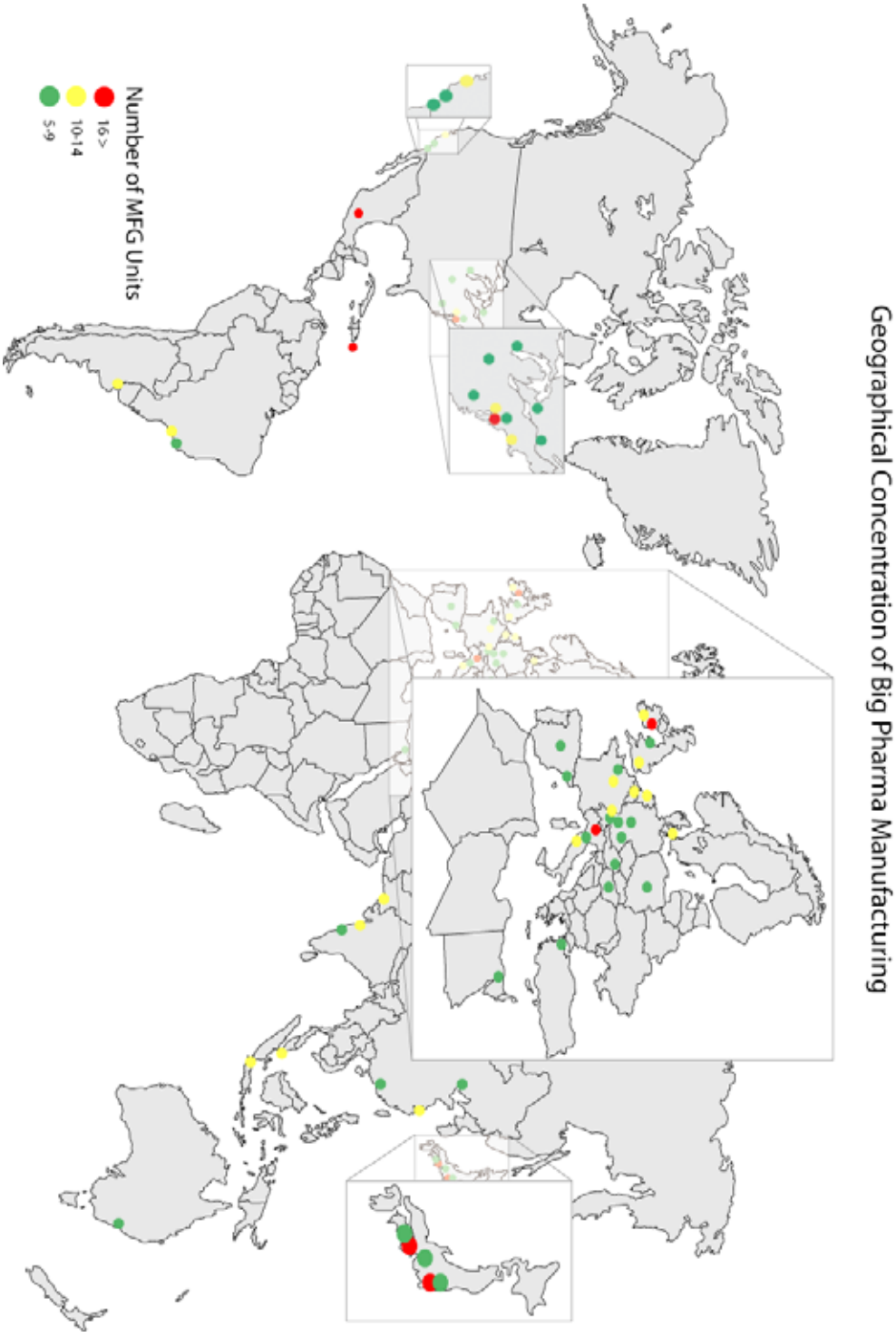
As for the R&D operations, the manufacturing units are mostly centred in North America, Western Europe, Japan, China, India, and Singapore. However, the manufacturing operations are more geographically dispersed, with a large number of countries having a minor big pharma presence. The presence in South America and Africa is higher than for the more knowledge-intensive R&D operations, even though these countries are still far behind the top countries in terms of number of manufacturing units present.

Figure 8: Top countries ranked by number of Manufacturing Units



The diagram in figure 9 shows the distribution of manufacturing units among the top countries, similar to the R&D units. The US (159) is at the top, followed by Japan (78), France (56), Germany (51), and Italy (47).

Figure 9: Concentration of Manufacturing Units shown as clusters



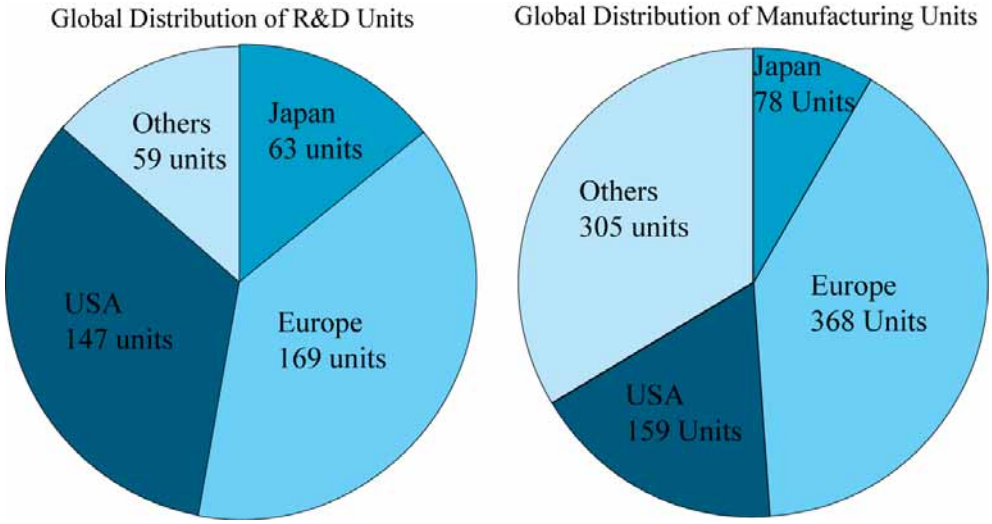
5.2.1 Manufacturing agglomerations

The cluster map in figure 9 has been created from the data collected on localisations of manufacturing units. There are strong concentrations in traditional OECD regions such as Europe (especially in Basel, Switzerland and Dublin, Ireland), in the US (around New York and Massachusetts, and California) and in Japan (particularly in Osaka and Tokyo).

5.3 Regional comparison

The diagrams below are a comparison based on a subset of the data collected in the empirical study, showing the distribution of R&D and manufacturing units in three important markets, namely the US, the European Union including Switzerland, and Japan. These represent 45%, 30% and 9% respectively of the world pharmaceutical market in 2006[32]. This comparison shows quite an even distribution between the US and Europe in terms of R&D units whereas for manufacturing units, Europe has almost twice as many as the US. Japan has around half the number of units compared to the US, in both categories. In manufacturing, the largest parts of the other slice are units located in China, India and Puerto Rico.

Figure 10: Comparison of the US, Europe and Japan



5.4 The big pharma geography of Sweden

The Swedish pharmaceutical industry has long been dominated by two major players AstraZeneca (formerly Astra) and Pfizer (formerly Pharmacia and Pharmacia Upjohn). Currently, AstraZeneca is conducting R&D in Södertälje, Mölndal and Lund and has manufacturing operations at two

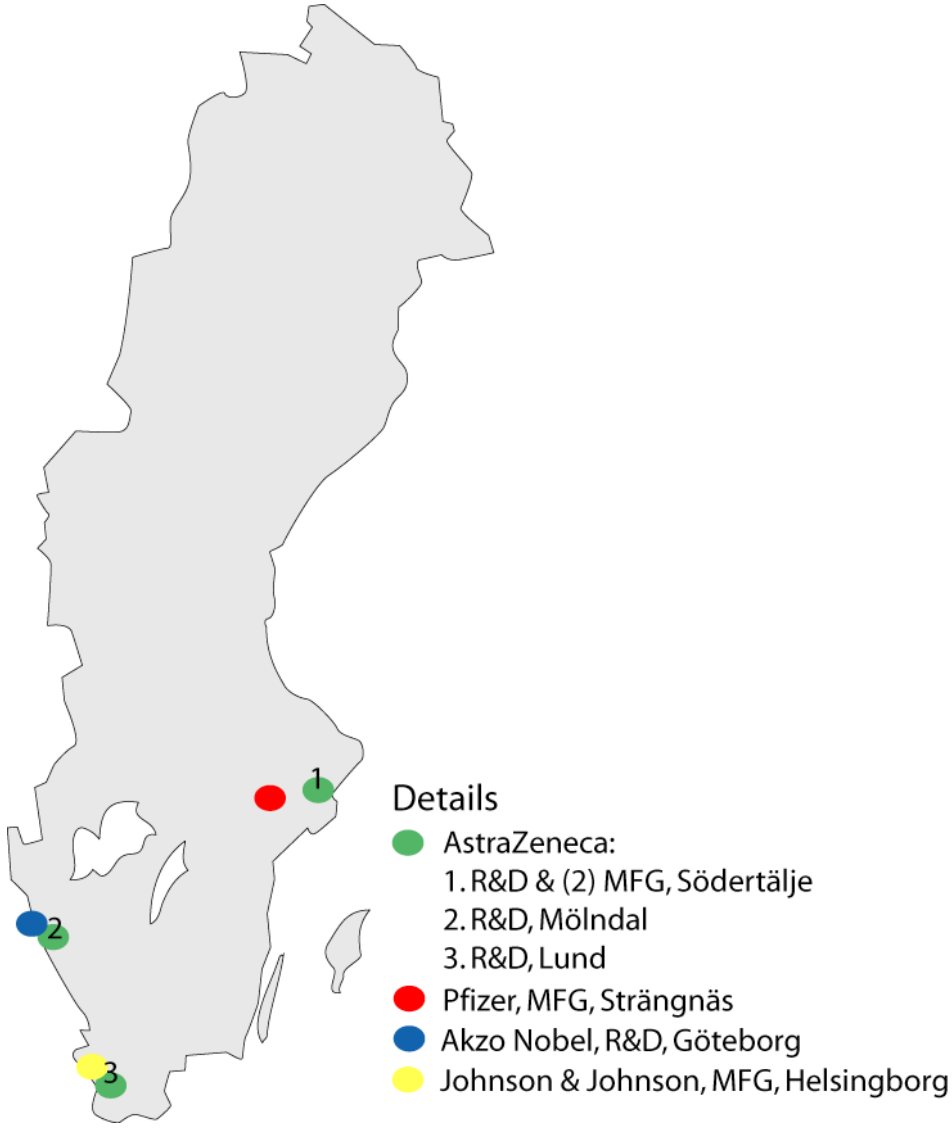
[32] *The pharmaceutical Market*, 2007, http://www.vfa.de/en/statistics/pharmaceuticalmarket/

plants in Södertälje. Pfizer has manufacturing units in Strängnäs and Stockholm (to be closed in 2008). Pfizer has also recently sold a manufacturing plant in Uppsala to Kemwell (2004) and a manufacturing plant in Helsingborg to Johnson&Johnson Consumer Healthcare (2007). According to the collected data big pharma has announced no plans for new units in Sweden; however, most of the current units have been expanded in the last five years, signalling a commitment to keep these locations active. An example of this is Pfizer's choice to expand the Strängnäs facility instead of closing it down, as was the original plan.

Today AstraZeneca is responsible for 78% of the Swedish pharmaceutical exports, accounting for SEK 46 billion out of a total SEK 59.3 billion (2006)[33]. The dependence on a single company is a risk. AstraZeneca has announced its intention to outsource some of the chemical production, potentially affecting some 400 jobs in Sweden. When and to what extent this will be done is yet to be decided. The current operations of big pharma in Sweden are illustrated in figure 11.

[33] *Verksamheten i Sverige*, 2007, http://www.astrazeneca.se/OmOss/Verksamheten-i-Sverige.aspx?mid=82 ; *Läkemedelsmarknaden 2007,* 2007, http://www.lif.se/cs/default.asp?id=15549 .

Figure 11: The big pharma geography of Sweden



6 Trends in Big Pharma Localisation[λ]

Analysing the results of the empirical study provides a view of the industry which can be compared over time. A number of trends can be observed in doing so, some of which will be presented in this chapter.

6.1 Global

The changes in geographical localisation can be divided into two parts – the start-up of new units and the closing of old units. The statistics on opened and closed plants have been compared over the last 10 years, e.g. from 1998 to 2007 and including plants under construction, planned for construction and planned for closure.

The closure of plants has been investigated as a part of the larger study. The data indicates that most plants are closed down in the US followed by Japan, France, Puerto Rico, the UK, and Ireland. In reviewing the empirical data, the closing of plants seems to correspond well with the total number of plants in the country, meaning there is no significant trend but rather a closing of a certain percentage of the active plants. Consistent with this, the US, the country with the largest big pharma presence, also has the most closures of old plants and founding of new ones. However, at least two significant divergences can be spotted – the trend towards closures in Puerto Rico and Japan.

In Puerto Rico, nearly 30% of the plants active ten years ago have been closed. Puerto Rico saw the beginning of its rise in the pharmaceutical industry some 40 years ago and since then has been home to a great many pharmaceutical manufacturing units for most of the major companies. Consequently, the last ten years have been a major switch. When the major companies established themselves in Puerto Rico the most important reasons were economic, such as tax incentives and other incentives given to foreign companies. However, this seems to be changing now; the old tax laws expire in the coming year and the decision-makers currently seem to be having a hard time agreeing a new set of laws[34]. This is making investors nervous, and might be a reason behind the closure of plants in Puerto Rico. Furthermore, the cost of electricity is rising, decreasing the economic

[34] Melia, 2007, http://www.mcall.com/business/local/all-puertorico.6144284nov17,0,6952768.story .

advantages of Puerto Rico. Other reasons cited by the companies in press releases are more general, and include excess capacity, expiry of patents and quality control issues. It is noteworthy that no R&D units are located in Puerto Rico, thus making it totally reliant on manufacturing.

Japan is one of the countries where the number of units has decreased the most over the past ten years. This can be largely attributed to increased consolidation in the Japanese pharmaceutical industry, where capacity has been optimised and slack removed as a result of mergers and acquisitions, creating a need to close excess units.

Some interesting trends can be found in the opening of new plants, the most important being a shift in the new localisation of the industry towards Asia. Similar to the closure of plants, the US is the country where the most new plants are started. However, next on the list are three relatively new players in the pharmaceutical industry: China, India and Singapore. These are followed by Ireland, Germany, Japan, and France. China, India and Singapore are relatively new entries on the pharmaceutical industry world map. China and India possess a large and well-educated workforce in addition to lower wages and tax incentives. Furthermore, the newly established units in these areas are not only manufacturing, but also R&D to a significant extent. The empirical study found that around 25% of the total units in China and India and 35% of those in Singapore are R&D units. Looking at the last ten years this number is even larger, close to 40% for all three countries. China and India will be further discussed in chapter 10, and Singapore will be discussed in chapter 9 about clusters.

6.2 Outsourcing

Presently, a number of the major companies are contemplating outsourcing of a significant part of their manufacturing operations, and both Pfizer[35] and AstraZeneca[36] have announced these intentions. In Pfizer's case the target is outsourcing mainly to Asia. The outsourcing trend is seen to a larger extent in manufacturing than in R&D operations. A reason for this focus on outsourcing is that manufacturing is not the core competency of these companies. According to Prahalad and Hamel, if this is the case, no competitive advantage is to be gained from it and it should be outsourced[37].

[35] 'Pfizer looks to Asia for manufacturing', 2007, http://money.cnn.com/2007/11/30/news/companies/pfizer_asia/index.htm .
[36] Pagnamenta, 2007, http://business.timesonline.co.uk/tol/business/industry_sectors/health/article2468741.ece
'AstraZeneca to outsource manufacturing', 2007, http://www.fiercepharma.com/story/astrazeneca-to-outsource-manufacturing/2007-09-17 .
[37] Prahalad & Hamel, 1990, pp. 79-91.

This view has been confirmed in two interviews with AstraZeneca managers with experience of the manufacturing organisation. They state that "there are no competitive advantages to be gained from manufacturing for AstraZeneca" [38]. Although this may be a little rash it still attests a view in the industry that the focus should be on research and commercialisation, whereas manufacturing is a necessity but of less strategic importance.

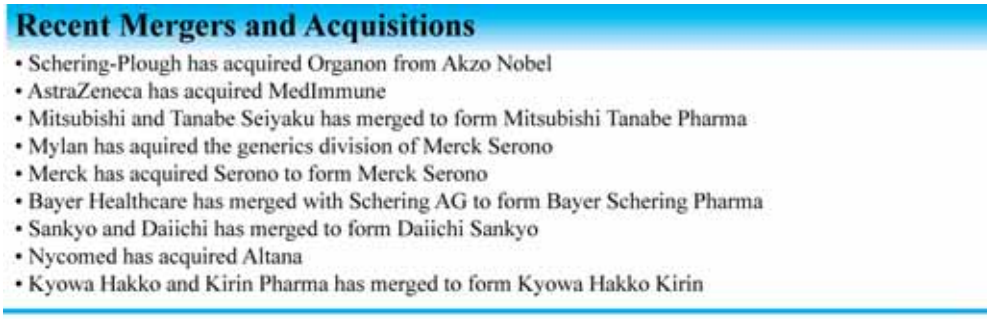
Also, the buying of smaller companies in order to acquire a patent or fill pipelines could be seen as an example of an increased R&D focus. However, in this case it is the research operations that are bought from external sources.

During the empirical study, it was also noted that a number of companies, mainly Japanese ones, have recently created subsidiaries to which all manufacturing has been transferred. This is also in line with the focus on core competencies.

6.3 Consolidation

Although the industry is dominated by a few major players, there is a vast number of other companies on the market. This can be illustrated by the relative market shares of the companies. The top ten companies were responsible for over 40% of the total industry sales in 2004[39], and continuing up the list, the top 20 companies are responsible for almost 60% of the total industry sales. A process of consolidation can be identified in the pharmaceutical industry; many companies have merged with others or acquired competitors to strengthen their positions. Some recent examples of the consolidation process can be seen in the mergers and acquisitions presented below.

Figure 12: Recent mergers and acquisitions



[38] Haeffler, (Project Director, AstraZeneca), [Interview], 2007;
Johansson, (Vice President of Supply and Capability, AstraZeneca), [Interview], 2007.
[39] Rosen, 2005, http://wistechnology.com/article.php?id=1903 .

The mergers and acquisitions in the pharmaceutical industry are usually driven by one of two main purposes. The companies are trying to either streamline their operations or acquire the pipeline of another company. The first category of mergers and acquisitions usually involves companies that are more comparable in size, such as the merger of Bayer Healthcare and Schering AG. The second category is usually a bigger company acquiring a smaller one which usually focusing purely on research but lacks the capabilities to commercialise its research. As the pharmaceutical product moves through the drug development process and gets closer to being a finished drug the costs get higher. In other words, the final steps of the development process are the most expensive; so expensive that in reality only the large pharmaceutical companies can afford them[40].

6.4 Generics

The traditional pharmaceutical companies, relying heavily on patents, are facing growing competition from generics companies. The generics companies are able to sell drugs more cheaply. This is mostly due to their having much lower research and development costs than the traditional pharmaceutical companies which sometimes spend over 20% of their revenues on R&D[41]. The generics sector is undergoing a globalisation, the prime example of this being the Israeli pharmaceutical company TEVA which is currently growing on a global scale, both organically and through acquisitions. Furthermore, an increase in the generics competitions is coming from the rapidly growing pharmaceutical industries of China and India. However, except for TEVA, these revenues of these generics companies are too low to be included in this study.

[40] Laestadius, 2007, [Personal communication].
[41] Rosen, 2005, http://wistechnology.com/article.php?id=1903 .

Analysis

This section will first present some localisation theory, followed by the authors' individual analyses of the data. The individual sections will be followed by a concluding discussion, areas for further study and conclusions drawn from this study.

7 Location Theory

This chapter presents some general concepts and theories regarding location of manufacturing and R&D operations. In addition to these theories will be related to the specific character of the pharmaceutical industry and exemplified by some of our results.

7.1 Location theory[θ]

Location Theory attempts to answer questions such as;

What are the reasons for firm localisation?

Or more specifically,

Why does firm A/B/C… locate in region 1/2/3…?

Needless to say there is no single theory that can give a satisfying answer to these questions, because people put different meaning into the word *firm* and *region*. If one sees the firm as merely adapting to the forces of the economy one would expect a different answer to the questions stated above than if one is supporting a view in which firms have the ability to act against such forces. Thus Location Theory is dependent on the *theory of the firm*.

Hayter[42] (1997), drawing on research by Machlup[43], identifies three general types of views on localisation following three different perspectives of the firm; the neoclassical, the behavioural and the institutional.[44]

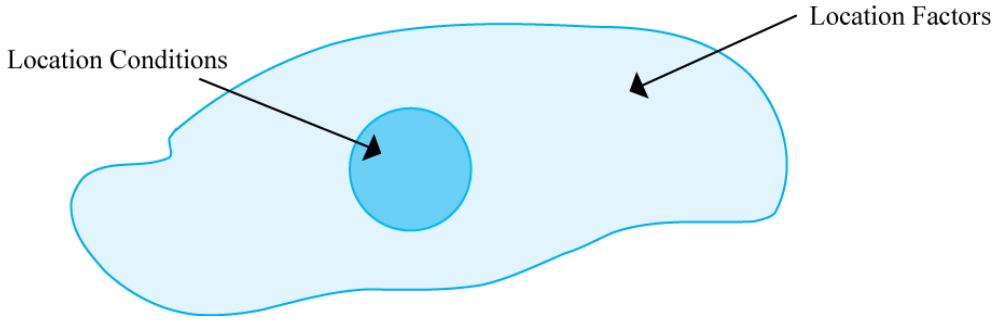
The neoclassical view sees location as a means to minimise cost and maximise profits. The firms act as *economic persons* adapting to the laws of demand and supply and location decisions are made automatically according to these. The behavioural theory puts greater focus on the decision-making process. A firm is acting as an economic person but only to the extent of what it knows. The firm can thus only survive and achieve its goals by gathering information about the surrounding environments and base its location decisions on these. The institutional theory regards the economy as being made up of actors with (sometimes) conflicting goals. Furthermore as

[42] Hayter, 1997.
[43] Machlup, 1967, pp. 1-33.
[44] Hayter, , 1997, p. 80.

firms are considered to possess some amount of power, the location decision is seen as a bargain between different regions and the firm.[45]

The environment in which a firm locates its activities can be characterised by different means. These region characteristics are usually called *location conditions* whereas *location factors* refer to a subset of the conditions that are of importance to the localisation of a specific firm[46].

Figure 13: Difference between location conditions and location factors



Source: R Hayter, The Dynamics of Industrial Location

There are multiple location conditions. Some of these can in a direct way be assigned a value, for example tax-levels, whereas other conditions such as competence of labour is much more difficult to measure. A summary of the different conditions is provided by Hayter[47].

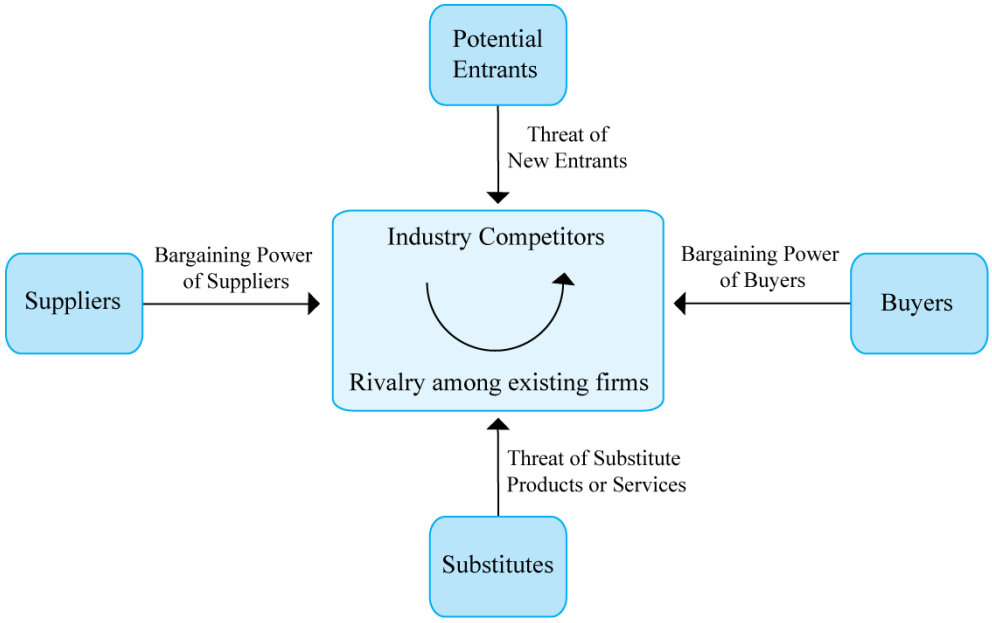
In this report the theoretical standpoint will be most similar to the institutional theory. That is, the geography of big pharma is regarded as a process which is influenced by different actors. Naturally big pharma themselves are central actors but so are also governments and regional organisations who by policies and regulations have the power to change the outcome of this geography as well as other players within the pharmaceutical industry.

7.2 Porter's five forces[λ]

The competition in an industry can, according to Michael Porter, be described using five forces of competition. This section will be based on this theory by Porter[48]. These forces vary in strength and are in the long run the determinants of profitability in the industry. In some industries the forces are favourable, the potential for long term profitability is larger, and as examples of this Porter mentions the pharmaceutical industry.

[45] Ibid.
[46] Nishioka & Krumme, 1973, pp. 195-205.
[47] Hayter, 1997.
[48] Porter, 1990.

Figure 14: Porter's Five Forces



Source: M E Porter, The Competitive advantage of nations

The threat of new entrants describes how hard or easy it is for a new competitor to enter the market, e.g. which entry barriers exist. Examples of such entry barriers could be: existence or absence of economies of scales, need for initial investments, access to technology, brand loyalty, government subsidies for new entrants and customer switching costs.

The threat of substitute products or services is basically the likelihood of the product being replaced by another product meeting the same customer demand. This is largely dependent on quality and cost, and their relationship. If the quality or cost of the substitute is better, a replacement is more likely, and if the price performance is better a substitution is probable. Furthermore, the switching cost between the two products is a relevant factor.

The bargaining power of suppliers or buyers is determined by the power of the supplier relative to the buyer. These forces are determined by such industry characteristics as number of buyer or suppliers, the switching costs between them, threat of backward or forward integration in the industry, and the profitability of the suppliers and buyers.

The rivalry among existing firms in the industry is largely affected by the characteristics of the industry, in terms of: the amount, size, and strategies of the players, the existence of high fixed costs, the possibility of product differentiation, and the extent of exit barriers.

Sometimes the government is also mentioned as one of the forces shaping the competition in an industry.

7.2.1 Porter's five forces in the pharmaceutical industry

There is a high degree of competition among the existing firms. There is also a possibility to gain first mover advantage by patenting new discoveries. Furthermore, the market is growing, providing possibilities to increase revenues without increasing market share.

The potential entrants are a weaker force, the main reasons for this are two. First, the barriers of entry are very high, and secondly the drug development process is extremely slow and costly.

The threat of substitutes is low as long as the product is protected by patent, thereafter this threat is increasing as generics manufacturing can be started. Also as discussed earlier, new discoveries in pharmacogenomics may provide opportunities for drugs that are more individualised.

The power of buyers is increasing due to recent pressure for decreases of drug prices. Also large organisation buying in bulk has the power to pressure the pharmaceutical manufacturers. To be noted is that when it comes to prescription drugs the end-users is not deciding which drug to use; this is done by a doctor (or in some cases by pharmacies).

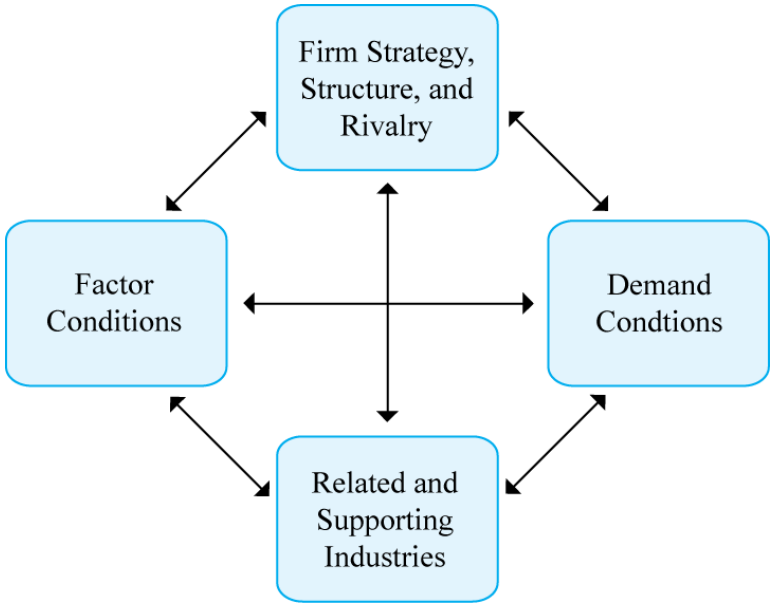
The power of the suppliers are generally low, since the product purchased from suppliers are most often commodities and the large pharmaceutical companies are able to achieve volume advantages. Furthermore, switching costs are low.

7.3 Determinants of national advantage[λ]

According to Porter, the factors determining the competitive advantage of a nation can be described by four groups of conditions shaping the environment in which companies compete, as shown in the image below. These factors explain why some nations are successful in a certain industry, and why some nations crash and burn. This section will summarise Porter's theory on the determinants of national advantage.[49]

[49] Porter, 1990.

Figure 15: Determinants of national advantage



Source: M E Porter, The Competitive advantage of nations

The factor conditions are factors of production, such as size, cost and characteristics of the personnel, infrastructure, geographical location, scientific and technical knowledge, availability of capital for financing, and political initiatives. These factors are the input needed, in order to compete in any industry. These factors can be further divided into basic and advanced factors, where the basic factors, such as unskilled workers and natural resources, require limited social or private investments and are not able to create a sustainable competitive advantage. Advanced factors on the other hand, such as highly educated workers, demand a higher investment and are significant for competitive advantage. The factors can also be divided into generalised and specific, indicating their specificity to a particular industry. Furthermore, these factor are not necessarily static or inherited, many of them can be changed, created or removed.

Demand conditions, composition of home demand is influencing the competitive environment by creating an advantage for nations where local firms are able to clearly identify the home demand better than foreign competitors. Important aspects of this factor are the size, segmentation, and sophistication of the demand.

In related industries sharing of certain aspects in the value chain are possible, such as technology or operational activities, or when products are complementary, such as computers and software. Related industries provide opportunities for exchange of information and technology, and also create opportunities for new entrants.

The source of advantage in the fourth category, firm strategy, structure and rivalry, is a match between the national characteristics and the sources of competitive advantage in a particular industry. This category includes how companies are created, organised and managed.

These factors are not only present as four distinct categories; there is also interaction between them shaping a dynamic environment. The creation of factor conditions is stimulated by a cluster of domestic rivals and related or supporting industries, whereas the priorities in creation of condition factors are influenced by the demand conditions. In the other way around, new entrants are created by favourable factor conditions and rivalling companies stimulate the emergence of related industries and suppliers.

7.4 Cluster theories$^{\Omega}$

All big pharma companies maintain several drug discovery research centres, of which a large number are located in geographic *clusters* of pharmaceutical research activity. The knowledge of research, especially the basic scientific, runs more rapidly and broadly to geographically nearby areas than to distant locations[50]. This observation is supported in the pharmaceutical industry by findings that pharmaceutical industries tend to locate in areas nearby well-known universities, thereby accessing world leading scientists[51]. In one way, universities enhance the stocks of knowledge and human investment through research and teaching, in another way, universities contribute to innovation in industry and economic growth. An obvious need for biopharmaceutical development is a high quality educational system and a highly skilled workforce.

The workforce is an important factor, pharmaceutical companies tends to invest in locations with adequate labour resources, which for instance can be seen in clusters. This permit direct observation of companies or cross-hiring, which can lead to maximizing job-matching opportunities and thus reducing search costs and generating competitive pressure to innovate[52]. Specifically, any region seeking to recruit, develop or maintain bio-pharmaceutical companies must have a highly skilled labour force in specific areas such as medical, biological, engineering and any related biopharmaceutical disciplines.

Research and development is crucial for the growth of the industry, it depends upon basic research. For this kind of industry with a long and expensive development process, taking 8-12 years and almost a billion

[50] Jaffe, Trajtenberg, & Henderson, 1993.
[51] Zucker, & Darby, 1997.
[52] Porter, 2004, pp. 65-67.

dollar, access to capital is therefore critical. The industry is dependent on federal government research funding and venture capital, localisation in such regions is therefore favourable[53]. The stability of the environment is critical for the localisation of pharmaceutical companies, this includes for example taxes, political stability, infrastructure, and labour cost considerations. Effective infrastructure is important to creative firms; it has been shown in the US that airport accessibility and direct flights is a high priority in the location decision.[54] Closeness to airport encourages services to clients, researchers from abroad and minimises travel time.

7.4.1 Definition of industry cluster

The majority of literature on industry clusters is agreeing on the following definition of a cluster: "*Companies with the same function and with similar production in focus, in geographic proximity that gain performance advantages through co-location"*.[55] The companies in a cluster are often competitors, but they interact and are often jointly networking. They have the same workforce in centre; they use the infrastructure in a similar way and have the same suppliers.

7.4.2 Porter's cluster-based strategy

Porter's strategy is based on the idea that the geographical proximity of companies within the same field creates *competitive advantage* for these companies.

In Porter's analysis he presents a simple definition of two types of clusters: vertical clusters, and horizontal clusters. Vertical clusters are made up of companies that are linked in some ways, such as through buyer-seller relations, while horizontal clusters comprise industries that might share a common market, have the same workforce or require similar resources.

Clusters enhance the efficiency, innovativeness, effectiveness and job creation of the companies in areas which they are located. The fact that the companies and universities are geographically proximate, permit movement of ideas and people between them, which encourage innovation. While Porter's theory focuses on strong competition, it also emphasises the cooperation between the firms. According to Porter, clusters symbolise a combination of competition and cooperation. Strong competition occurs in winning customers and keeping hold of them[56].

[53] Dibner, 2001.
[54] Echeverri-Carroll, 1999.
[55] Doeringer & Terkla, 1995, pp. 225-237.
[56] Porter, 1990.

7.4.3 Cluster growth and development

What drives the industry cluster development and growth is a common subject discussed in literature. In general, companies locate according to the greatest economic advantage. Such advantages can either depend on access to a specific market or a relevantly skilled workforce. Porter argues that competition is the main factor driving cluster development; the competition between challenger firms drives growth since it forces the firms to be innovative and create new development, such as new technology. This in turn stimulates R&D and stimulates the introduction of new expertises and services. Since companies within the cluster have a similar labour force, the employees can move from a company to another and transferring knowledge to other firms and promote more competition and for that reason growth.

7.4.4 Industry cluster policy

Industry cluster policies can also play a significant role for industry targeting and employment, since the industry is dependent on research funding and environment stability. Cluster policies are believed to inspire competition, which in turn leads to economic growth. Clusters can also expand an economic base, by generating the specialised supplier networks to serve the larger companies in the cluster[57]. Even though cluster policy is important, there are some general criticisms of cluster policies, Rosenfeld present some points[58]:

- One of the major concerns is that if the companies in the cluster fail, then the economy of the entire region is ruined.
- Another criticism is that industry cluster policies are more adapted to small, specialised firms than large, multi-national firms since they already dominate the existing economy.
- A third disapproval is that industry cluster policies only apply to urban areas rather than rural areas since industry activity is too geographically scattered.

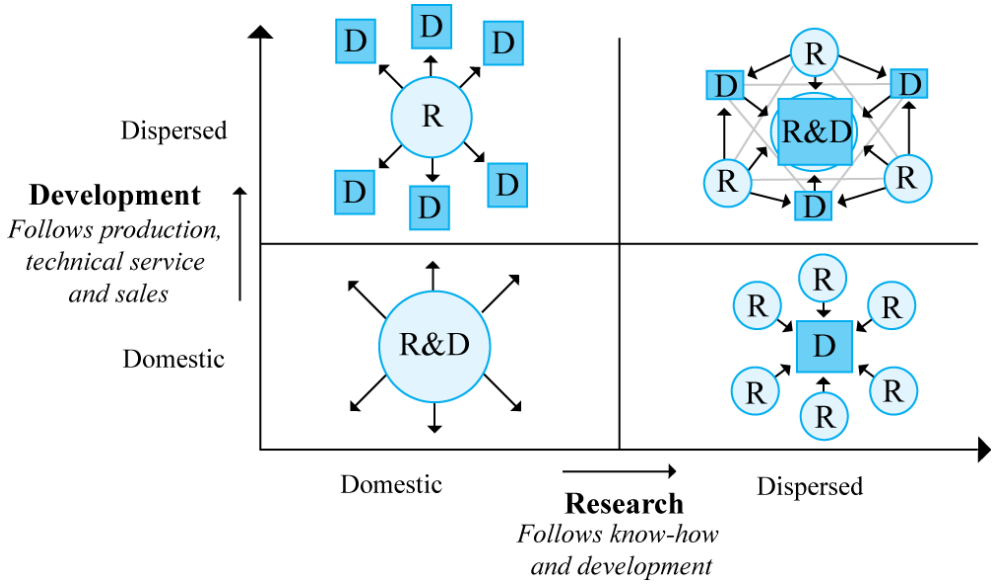
7.5 R&D internationalisation$^{\lambda}$

As a description of R&D in the pharmaceutical industry, especially in the largest companies, Gassman and von Zedtwitz' model of R&D internationalisation can be used. According to this model research (R) and development (D) can be organised in one out of four ways. The research units can be geographically centred (domestic) or geographically scattered

[57] Doeringer & Terkla, 1995, pp. 225-237.
[58] Rosenfeld, 1995.

(dispersed), and in the same manner the development units can be either domestic or dispersed, thus creating a matrix with four possible forms of R&D organisation.[59]

Figure 16: Model of R&D Internationalisation



Source: M von Zedtwitz & O Gassman, "Market versus technology drive in R&D internationalisation: four different patterns of managing research and development

As an explanation for these four types of organisation, Gassman and von Zedtwitz describes two main drivers, localisation of research units is driven by technology and localisation of development units is driven by proximity to market where the product is sold. Technology in this sense is referring to access to technology, such as availability of a highly competent workforce and closeness to scientific centres. Proximity to market is a factor for development units, because of the importance of developing a product for a specific market or group of customers. These drivers are not specific for the pharmaceutical industry, but seem to fit well with the view of the industry presented in the empirical data.[60]

[59] von Zedtwitz & Gassman, 2002, pp. 569–588.
[60] von Zedtwitz, & Gassman, , 1998.

8 Localisation in the Pharmaceutical Industry[λ]

This chapter seeks to provide a view of important reasons for localisation of manufacturing, R&D and biotech operations. Furthermore, some examples from the results of the empirical study are shown.

8.1 R&D localisation in the pharmaceutical industry

In the pharmaceutical industry research is the process of discovering lead compounds and taking them up to the point where preclinical testing begins. Whereas development is the process beginning with preclinical testing until the drug is commercially producible.

In general the major players in the pharmaceutical industry are highly internationalised companies both in manufacturing, research and development, thus the general view of these companies is that of a global R&D organisation. As for smaller companies the research is increasingly domestic or geographically centralised, a market driven R&D organisation. For even smaller companies the development as well is centralised, a national treasure R&D organisation. The companies of interest in this study can all be sorted into two of the categories explained by Gassman and von Zedtwitz, either global R&D organisation (both research and development are internationally dispersed) or market driven R&D organisation (dispersed development and domestic research).

More specific for the pharmaceutical industry location of development operations, is the fact that a great many countries demand clinical trials to be conducted on its own population before the drug is approved for sales in the country. This forces pharmaceutical company to keep their development organisation geographically dispersed, creating a global organisation.

According to literature an exception to the global R&D organisation is the Japanese pharmaceutical companies which to a higher degree than the European or American companies rely on a domestic research and development organisation. However, according to our results this view must be challenged. The Japanese companies have clear concentration of the R&D effort in Japan, but a large amount of their R&D resources are also located elsewhere. A part of the explanation for this may be a growth of the companies in terms of sales as well as in the number of markets served.

The view of research localisation as being first and foremost driven by access to competence or technology seems to be common ground in this

field of research. Furthermore, this is well in line with the empirical study showing a clear pattern that research units are located in proximity to centres of research with a competent workforce. Simplified, this localisation is driven by access to technology, in the form of a well-educated competent staff and centres of scientific excellence, such as prominent universities. Examples of this organisational behaviour can be seen in the concentration of pharmaceutical research units in areas that fits the criteria above, such as Cambridge (USA), Cambridge (United Kingdom), and San Francisco (USA), that is observed in the empirical study.

The cost aspect of an R&D localisation is usually not the key issue, however for simpler processes demanding a lower degree of specific competence a higher cost focus can be found since there are a larger number of location able to live up to the demands for competence.[61]

8.2 Localisation of manufacturing

Compared to R&D the localisation of pharmaceutical manufacturing has a different set of drivers. The manufacturing is to a lesser extent dependent on a high competence and local scientific excellence, instead the focus is more on regional properties – both tangible and intangible. The manufacturing could be divided into four categories, the chemical, the biological or biotechnological, the formulation (fill-and-finish) and packaging (packaging is excluded in this study). The chemical and biotechnological processes are generally more centralised to fewer locations and the formulation part of the production is usually more market driven. Because of the difference between the different steps in the manufacturing process a generalised set of drivers may be hard to establish, however a number of criteria can be identified.

Possibly the most important parameter in localisation decisions is the tax system combined with the judicial system.[62] Since most of the value in the manufacturing process is created in the chemical or biotechnological phase, this is where taxes makes the largest difference, this has given rise to manufacturing clusters in regions with favourable taxes, such as Ireland and Puerto Rico. Furthermore, protection for intellectual property is an important factor, in this industry with a high demand for patent protection. This factor has been in focus when establishing in new economies, for example in China where intellectual property protection is weak. Also many regions are giving economic incentives to companies that are establishing operations in the region, such as lower taxes.

[61] NERA Economic Consulting. 2007.
[62] Ibid.

Obviously, a workforce is needed to operate a plant, however these tasks do not need the same highly competent scientific workforce as in the R&D phase. An adequately skilled workforce can be found all over the world, and this is usually not the major issue. However, laws regulating the job market are of higher importance, providing flexibility for the company.

Basically, the intangible prerequisites mostly concern the minimizing of costs relating to the manufacturing. Whereas the criteria for R&D localisation are in a higher degree concerned of the available competence.

Among the more physical properties of a location are the transport infrastructure and the more basic features, such as availability of electricity and water. The produced goods need to be transported from the factory, thus creating a need for proximity to transport infrastructure. Furthermore, fast and flexible means of personal transportation is important in the global economy of today, thus giving rise to a need for access to international airports.[63]

Also important are factors affecting the quality of life for the staff. This could include quality of schools, general surroundings, availability of housing, and standard of hospitals in the area. Furthermore, biotechnological or pharmaceutical companies also require specifically configured laboratories, both for R&D and manufacturing. [64]

8.3 Localisation of biotech operations

Localisation of biotechnological production has largely the same drivers as the rest of the production, however it is more dependent on the competence of the workforce, because of the higher technological level of these operations. Another important issue is that biotechnological production is harder to transfer to a new plant, thereby providing incentives for keeping an established plant and producing the drug at the same place for the life time of the drug. A setup that works at one location does not necessarily work and give the same results at another place.

The new localisations of biotechnological production are scattered, but it has been found that most of them are in the US. Canada and Singapore are also important locations for new biotechnological factories. Notable from the study is that this particular type of production seems to be less frequently located in low cost countries, probably because of the greater technological demands which dictate dependence on a higher skilled workforce.

[63] Eklund, Hallencreutz, & Lindqvist, 2007.
[64] Ibid.

9 The Ideal Company$^{\lambda}$

A comparison between the real world and an *ideal* case will be presented in this section in order to analyse the reasoning about localisation and determine the degree to which localisations are governed by rational and logic consideration. The comparison was conducted by comparing the data collected for this study with a corporate view of how the ideal company would be geographically located. A recent study conducted by NERA Economic Consulting[65] (published September 2007) had 34 chief or senior executives from 14 pharmaceutical companies do a case letting them construct the ideal pharmaceutical company. The scenario given to them was as follows:

> *A medium-sized research-based pharmaceutical company has an opportunity to re-establish itself without taking history into account. How would it divide its assets and where would it locate them?*[66]

The executives represent 13 companies from the top 35 pharmaceutical companies based on revenues, including eight of the top ten companies, and one company outside the top 50 list. The companies are globally divided, consisting of six American, two British, two Swiss, two German, one French, and one Japanese company. This study is not to be seen as a definitive truth. However, since it is based on the views of executives in large pharmaceutical companies, it should give some indication as to how they view the ideal localisation of a pharmaceutical company.

The results of the above mentioned study show a picture of the "ideal" company with clear similarities to the recent trends in the industry. The answers of the executives are shown in the figure below. What may be most surprising is the manufacturing unit located in Portugal, a country with a quite limited big pharma presence; according to the empirical results only five manufacturing units are located in Portugal. One reason for this may be the lower wage levels and relatively low corporation tax in Portugal compared to many other Western European countries.

[65] NERA Economic Consulting, 2007.
[66] Ibid.

Figure 17: The ideal pharmaceutical company

Source: NERA Economic Consulting, Key Factors in Attracting Internationally Mobile Investments by the Research-Based pharmaceutical Industry

Based on these answers provided in the report from NERA Economic Consulting, a comparison was made with the empirical data collected in this study. This comparison could show indications about the rationality of location decision, providing a hint about such things as the role of history in new establishments. First of all, according to the empirical study the "real" pharmaceutical company with five manufacturing units and six R&D units would be distributed as shown in the following figures. It is based on the top locations found in the empirical study, e.g. the location with the largest number of established units. Figure 17 shows the distribution based on the entire study, while figure 18 is based on a sample consisting only of units started in the last ten years, i.e. between 1998 and 2007. The locations in italics are the ones which differ between the *ideal* and the *real* company.

Figure 18: The real pharmaceutical company

Figure 19: real pharmaceutical company 1998-2007

As seen in the comparison, the new establishments during the last ten years seem to correspond well with the view of the ideal company from the NERA report. Which is logical since these localisation decisions should follow the view of the executives, and should be part of the same paradigm in pharmaceutical localisation. However, regarding all the units found in this study, the differences are larger especially for manufacturing units. Reasons for this could be that the drivers have changed over the course of the 20th Century, the world has become increasingly globalised and that the history of the company still plays an important role when choosing new locations. Generally, the R&D units correspond better to the idea of the ideal company. One reason for this may be that the manufacturing units are more geographically scattered.

The impact of the history can be manifested in several ways. The company generally has some sort of commitment to its home region, for example AstraZeneca maintains a strong presence in Sweden. This commitment could be explained by several factors, such as cultural or tradition-based reasons and that previous investment binds the company to the region. Furthermore, previous investment in a region may also have created an increased competence, thus making the region more attractive for future investment in related fields, for the particular company as well as others.

In conclusion, the recent establishment of new units converges with the view of the ideal company as presented by NERA Economic Consulting based on interviews with chief and senior executives of the 14 large pharmaceutical companies. This is logical, but of more interest is the divergence between the older localisations and the idea of the ideal company. The impact of history may be one reason for this. Another may be the changes that have occurred in the industry and in the world economy altering the drivers and regional conditions governing localisation. The historical impact has several aspects, one may be a sentimental connection to the area, and another more rational aspect could be benefits gained from being localised in proximity to previous units within the company.

10 Location of Big Pharma R&D in Europe[θ]

Big pharma is R&D-intensive enterprises whose ultimate survival depend on discovering, producing and marketing drugs. These companies are actors on a global market with operations mainly in Asia, America and Europe. Furthermore the scientific and technological advances are processes influencing the pharmaceutical industry on a global scale.

Due to the 'globalness' of the study object, it would be relevant to search for explanations for the localisation of big pharma in globalisation theory. Such a theoretical framework has been developed by Peter Dicken in *Global Shift*.[67] According to Dicken:

> *(…) the globalization of economic activity arises from the dynamic interplay between three sets of processes: the strategies of TNCs, the strategies of national governments and the character and direction and nature of technological change. But precisely how these processes operate, and the specific outcomes produced, varies substantially between different types of economic activity.*[68]

No doubt big pharma are transnational corporations (TNCs) in the sense that they have "the power to coordinate and control operations in more than one country"[69]. Thus, explaining the geography of big pharma R&D would be most likely linked to the *strategies of TNCs*. However, particularly within the R&D-intensive pharmaceutical industry, these strategies are influenced by *the strategies of national governments* and *the character, direction and nature of technological change.*

Big pharma location is influenced by the strategies of national governments in the sense that the industry is highly regulated. Furthermore the policies adopted by nation-states and international collaborations, such as the EU, have the power to change the contours of the map on which TNCs base their location decisions.[70]

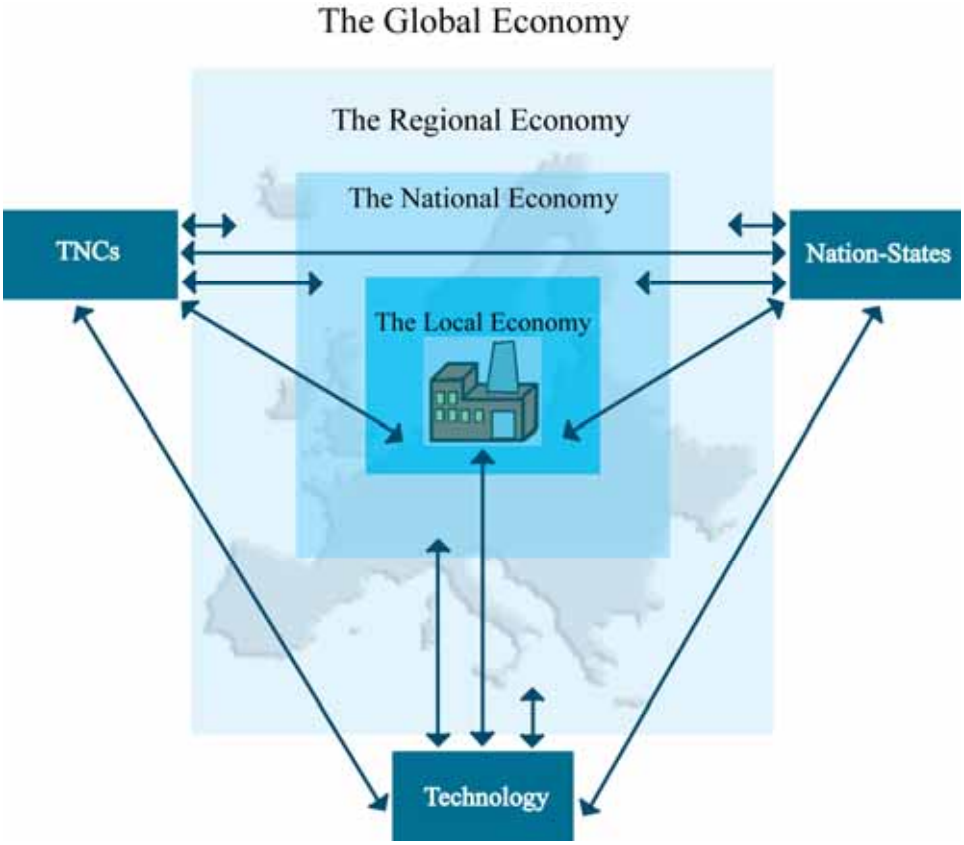
The character of technological change has a strong influence on the location of big pharma R&D units because TNCs are highly dependent upon

[67] Dicken, 2003.
[68] Ibid., pp. 4. Author's italics converted to underlining.
[69] Ibid., pp. 198.
[70] Dicken, 1992, pp. 303-316.

innovation[71]. In the end, it is through such innovations – the discovery of new drugs – that big pharma makes profits.

Moreover, every location should be understood by the characteristics of its local, regional and global context as well as in the light of technological change, the strategies of nation-states and the strategies of TNCs. Figure 19 summarises these relationships:

Figure 20: The Global Economy



Source: P Dicken, Global Shift: Reshaping The Global Economic Map in The 21st Century

10.1 Purpose

The intention in this chapter is to outline some aspects of the theory presented in Peter Dicken's *Global Shift*[72] and discuss it in relation to the geography of big pharma R&D units in Europe: Can the character of technology and the strategies of TNCs and nation-states explain the location of big pharma R&D?

[71] Dicken, 2003.
[72] Dicken, 2003.

Following this brief discussion, a hypothesis of how big pharma location has been affected by one of these three drivers will be presented. More specifically, this hypothesis will focus on the *molecular biology revolution* and how it has affected geography of big pharma R&D activity in Europe.

10.2 Delimitations

Due to time constraints, the focus of this chapter is on the big pharma R&D units within the *European region* (EU-27[73] + Switzerland). Thus the study is limited to the 169 R&D units that have been found within these countries. None of the closed plants will be considered due to the fact that this information is far from complete.

Scientific advances in genetics, genetic engineering, peptide chemistry and cell biology are at the core of the *molecular biology revolution*[74]. This revolution should not be seen as a historical event with a fixed beginning and end. Some authors[75] claim the revolution started by the famous discovery of the double-helix structure of DNA by Watson and Crick in 1953 whereas some[76] refer to the first biotechnological application by Herb and Boyer in 1973.

In this chapter, the molecular biology revolution will be presented only in the particular aspects relevant to advancements in the pharmaceutical industry. It is seen as an ongoing process beginning sometime in the early 70s,

10.3 Method

The outline of this chapter consists of a presentation of some of the aspects of the theory as outlined by Dicken in *Global Shift*[77]. This will be followed by a brief discussion of how each of the three main forces in the global economy have affected the geography of big pharma R&D in Europe. Where possible, this will be exemplified by empirical data.

It should be noted that it is very difficult to discuss these interrelated drivers separately. Moreover it is difficult not to discuss the European region in the absence of the rest of the world. However, the ambition in this chapter is to

[73] EU-27: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.
[74] Henderson, Orsenigo & Pisano, 1999.
[75] Ibid.
[76] ABC Online, http://www.abc.net.au/science/features/biotech/1970.htm
[77] Dicken, 2003.

keep the discussion about the theoretical entities separate and relate this to the European region.

The focus of this chapter will then turn on a particular aspect of the nature of technological change within the pharmaceutical industry. This discussion will result in a hypothesis connected to the revolution in molecular biology and its consequences for the spatial distribution of big pharma R&D. This hypothesis will be tested by a method designed to make use of the empirical data of big pharma R&D units. Results will then be presented and discussed. Finally, there will be some remarks on how to explore and make use of this data for further studies.

10.4 Theory

In this section, some aspects of Peter Dicken's[78] three main shapers of the global economy will be presented.

10.4.1 Strategies of TNCs

Dicken defines TNCs in the following manner:

> *"A transnational corporation is a firm that has the power to coordinate and control operations in more than one country".*[79]

10.4.1.1 The geography of R&D facilities

TNCs are in need of extensive research and development efforts to keep up with the competition on a world market. Corporations can choose to have a few concentrated R&D activities or locate these closer to other functional units or markets. There are advantages and disadvantages with each strategy.

Dicken asserts that the location of R&D facilities varies according to its specific market orientation:

- TNCs with a strong *home market* orientation tend to carry out little foreign R&D other than of the support laboratory type. Such firms tend to regard their foreign sales as not requiring any further R&D beyond that carried out for their domestic market.
- *Host-market* TNCs – those oriented towards the national (or regional) market in which their foreign operations are located – operate both support laboratories and also higher-level locally integrated laboratories. The most important locational criteria are proximity to the firm's foreign markets and the fact that the firm's foreign operations are sufficiently

[78] Ibid.
[79] Ibid., pp. 198.

substantial to justify separate R&D activities. Such activities tend to be located in the firm's biggest and most important foreign markets

- *Global-market* firms are the globally integrated corporations whose orientation is to global, rather than national, markets. Their R&D activities include both support and locally integrated laboratories but, in addition, their adoption of a globally integrated production strategy leads them to establish specially designed international interdependent research laboratories. The major locational criteria for these global-market R&D activities are the availability of highly skilled scientists and engineers, access to sources of basic scientific and technical developments – especially of high-quality universities – and an appropriate infrastructure. [80]

The exact configuration of R&D units depends to a large part of the organisational structure of the TNC as a whole. If a hierarchical style is used, the firm is more likely to organise its R&D according to such fashion. If, on the other hand, the TNC has fewer such influences the organisation of R&D will be less centralised and more geographically dispersed.

The organisational structure depends in turn on the *specific history of the firm,* such as its *home-country embeddedness* and *cultural and administrative heritage,* and the nature and complexity of the *industry environment*.

There is disagreement on the extent TNCs locate R&D outside their home-country. In short, the reasons for keeping R&D activities within the home-country and close to headquarters are connected to the fact that the output of these involve uncertainty and that the information is person-embodied.[81] The reasons for maintaining international R&D activities are connected to the fact that key know-how is internationally dispersed.[82]

10.4.2 The strategies of national governments

Nation-states consist of a geographical containment in which a population with common cultural traits is organised by a common authority structure. Thus nation-states are containers of different types of resources with the ability to regulate activities within their boundaries. In that sense, nation-states are both *containers* of economic activities and *actors*. [83]

The exact composition of regulations (or strategy or policy) that a nation-state adopts depend on the following factors:

[80] Ibid., pp. 243. Author's italics converted to underlines.
[81] Patel, 1995, pp. 141-153.
[82] Hotz-Hart, 2000.
[83] Dicken, 2003, pp. 123

- The nation's political or cultural complexion and the strength of institutions and interest groups.
- The size of the national economy, especially that of the domestic market.
- The nation's resource endowment.
- The nation's relative position in the world economy, including its level of economic development and degree of industrialization.

There are essentially two types of macroeconomic policies that can be pursued by governments. *Fiscal policies* are used to regulate taxes on companies and citizens and to decide on government expenditure. *Monetary policies* are used to regulate the circulation of money within the economy, usually by means of manipulating interest rates.

10.4.2.1 Trade policies

Nation-states have the ability to impose different barriers toward imports of products and services into the country. *Tariffs* are taxes put on imports as a means of reducing their competitive advantage in comparison to domestic goods. *Non-tariffs* are restrictions on imports of a diverse nature; they can be technical (licences required) or quantitative (quotas).

Export policies are used to provide incentives for the industry to sell its goods to foreign markets. These policies include a variety of measures such as *export credits and guarantees*, *operation of overseas export promotion agencies* and *establishment of export processing zones and/or free trade zones*.[84]

10.4.2.2 Foreign direct investment (FDI) policies

The internationalisation of the economy has increasingly made governments aware of restrictions and incentives on foreign investment. Dicken summarise these policies in four broad categories:

- *Entry*. Governments may decide to regulate the establishment of foreign firms by different measures. It can for example uphold laws on the extent to which companies can be owned by foreign companies.
- *Operations*. Nation-states can set up rules for the local content of operations in terms of involvement with local contractors or suppliers. Thus, the government will ensure some positive externalities in terms of employment and increased economic activity
- *Corporate profits and the transfer of capital*. Governments may impose taxes on foreign-owned firms so as to gain access to some of the profits made within national borders. Conversely, international enterprises wish to minimise such taxes so as to maximise their own profits.

[84] Ibid., pp. 132

- *Stimulate*. Due to the increasing global dimensions of the economy, governments may try to attract foreign investment as part of their competition with other nations. This can be done by introducing incentives and bidding in an international, national or regional bargaining process.

10.4.2.3 Industry policies

There are numerous policies by which governments can regulate economic activity. Such policies can be directed either generally, affecting all firms, or selectively at a certain type of activity or a geographical region.

These include[85]:

- Investment incentives:
  Capital-related
  Tax-related
- Labour policies:
  Subsidiaries
  Training
- State procurement policies
- Technology policies
- Small firm policies
- Policies to encourage industrial restructuring
- Policies to promote investment
- Merger and competition policies
- Company legislation
- Taxation policies
- Labour market regulation:
  Labour union legislation
  Immigration policies
- National technical and product standards
- State ownership of production assets
- Environmental regulations
- Health and safety regulations.

10.4.3 The character of technological change

Technological change has a profound influence on the way economic activity is organised because innovations enable the creation of new structures, institutions and products.[86]

[85] Ibid., pp. 139.

The creation of technology, innovation, depends on the accumulation and adaptation of new knowledge. In general, knowledge can be defined as either *codified* or *tacit*. The former is the type of knowledge found in books or software. Such knowledge can travel great distances by means of the Internet or other transportation or communication systems. Tacit knowledge on the other hand is difficult or even impossible to spread over greater distances because it cannot be formalised. Due to the *localness* of tacit knowledge, it is important to outline the characteristics of the environment in which it is embedded. Dicken distinguishes three such characteristics of what he calls the *innovative milieu*:

- the economic, social and political institutions themselves
- the knowledge and know-how which evolves over time in a specific context (…)
- the 'conventions, which are taken-for-granted rules and routines between the partners in different kinds of relations defined by uncertainty'[87]

Evidence suggests that national context can have a considerable impact on how such milieus are composed[88]. Within nations, local agglomerations of economic activity, *clusters*, exist. According to Dicken, the reason for the existence of clusters can be understood in the characteristics of the innovation process:

- *Localized patterns of communication*. Geographical distance greatly influences the likelihood of individuals within and between organizations sharing knowledge and information links.
- *Localized innovation search and scanning patterns*. Geographical proximity influences the nature of a firm's search process for technological inputs or possible collaborators. Small firms, in particular, often have a geographically narrower 'scanning field' than larger firms.
- *Localized invention and learning patterns*. Innovations often occur in response to specific local problems. Processes of 'learning by doing' and 'learning by using' tend to be closely related to physical proximity in the production process.
- *Localized knowledge sharing*. Because the acquisition and communication of tacit knowledge is strongly localized geographically there is a tendency for localized 'knowledge pools' to develop around specific activities.

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[86] Ibid., pp. 85.
[87] Ibid., pp. 116.
[88] For reviews of national innovation systems see for example Lundvall & Maskell (2000).

- *Localized patterns of innovation capabilities and performance*. Geographical proximity, in enriching the depth of particular knowledge and its use, can reduce the risk and uncertainty of innovation.[89]

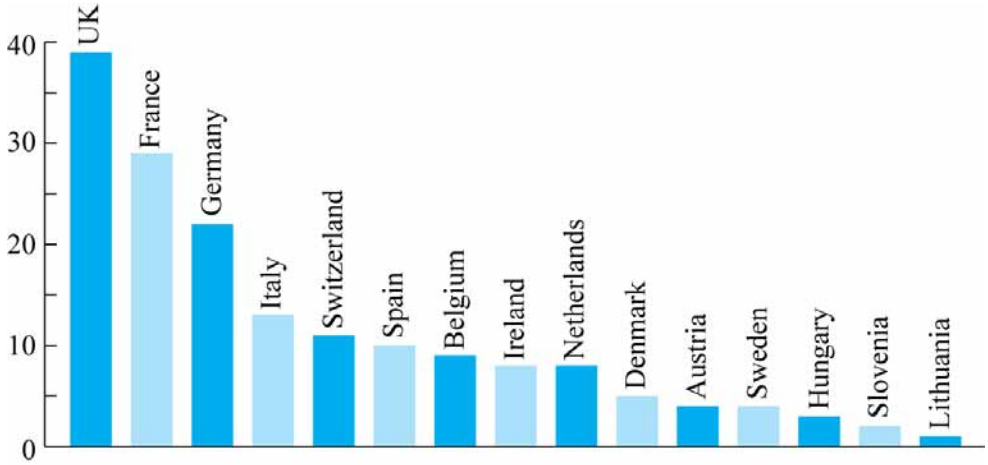
These milieus gain their momentum in the *path-dependency* of technological change. Thus, most acclaimed clusters are a result of a historical growth process and not the conscious creations of governments or other policy makers[90].

10.5 Explaining the geography of big pharma R&D in Europe

From the theoretical outlay, there are some observations which can be discussed in relation to the geography of big pharma R&D units.

The big pharma R&D units in Europe are distributed as follows:

Figure 21: Number of big pharma R&D units in Europe by country



It should be stressed that the data only contains the *number* of R&D units within each countries. There is no appreciation of the size of these units in terms of monetary *value* or *workforce*. Thus, one should be cautious in drawing overly far reaching conclusions based on this data. Furthermore, the data presented is a snapshot of the number of units presently located in these countries. Some of these R&D units were established in the 19th Century and some were opened this year (2007). Thus, to understand the snapshot of big pharma R&D units visible today, we need to understand the historical context of the pharmaceutical industry.

[89] Dicken, 2003, pp. 116-117. Author's italics converted to underlining.
[90] Ibid., pp. 117.

10.5.1 The strategies of big pharma

Big pharma equals *global-market* firms in the sense that their products (the drugs) are sold on global rather than specific national markets. Thus, theory suggests that the R&D units are of a global market character and key location factors are availability of skilled scientists and access to sources of basic technical developments and infrastructure. Indeed, it has already been shown that big pharma R&D units tend to be located near acclaimed universities etc. To some extent, this may explain the large amount of R&D units within the UK for example. In fact a fair proportion of these units are located near Cambridge University and London University.

Dicken stipulates that the dispersal of R&D units is coupled to the organisational form of the specific company. Disappointingly, no uniform organisational structure typical of big pharma chosen has been chosen for our study. The reason for this is obvious; the companies were not selected on such grounds and they thus differ greatly in the factors that, according to Dicken, influence the particular organisational structure adopted. The most obvious difference in such terms is that they have been grown in a variety of historical contexts and national, regional, and local environments.

The actual share of R&D operations being located outside the home economy can be seen as a trade-off between the importance of control versus the importance of internationally dispersed know-how. On average, the companies in our study retain 40% of the R&D units within the home country. These low numbers in comparison to other TNC studies[91] suggest that big pharma locates internationally, and that scattered know-how is more important than the specific advantages of locating most research efforts close to headquarters. Indeed, most big pharma companies maintain R&D operations in Japan, America and Europe. On the contrary, most big pharma companies also have strong research centres in their host countries. Thus, one would expect the proportion of domestic R&D in terms of investments or workforce to be somewhat larger than the proportion of number of R&D units.

The European countries with domestic big pharma are Germany (3), Switzerland (3), the UK (3), Belgium (2), Denmark (2), France (1) and the Netherlands (1). The European companies only retain about 20% of R&D units in the country where their headquarters are located. Thus, there is an even lower correlation between the number of big pharma companies with headquarters in a country and the number of R&D units than for the whole sample. However, this can partly be explained by the fact that European nations are smaller markets than the US and Japan and that much European

[91] Patel, 1995, pp. 141-153.

big pharma is historically linked to other European pharmaceutical companies. One example is the merger of Swedish Astra and British Zeneca into AstraZeneca.

10.5.2 The strategies of national governments

While it is far from possible to assess every national policy within this brief discussion some general points can be made about the connection between the role of national governments as *actor* and the 'amount' of big pharma they *contain*.

Switzerland and Ireland are among the *successful* countries when it comes to attracting R&D-intensive pharmaceutical industry. Indeed, these countries have relatively high numbers of big pharma R&D units in relation to their population and GNP.

It is well known that ever since *opening* its economy in the 50s, Ireland perhaps more than any other European country has adopted aggressive policies to attract inward investment. Many pharmaceutical firms have had long established manufacturing operations in Ireland. Presently, 40 big pharma manufacturing facilities are located there. However, there have been concerns that such policies would not lead to any significant input into the Irish economy other than temporary employment.[92] According to our results, big pharma has started to locate a fair amount of R&D units in Ireland. The total number of R&D units is eight, five of which have been located during the 21st Century.

Switzerland has a profound history within the pharmaceutical industry. Chemical processing companies and dye manufacturers such as Ciba and Sandoz were among the pioneers at the birth of the pharmaceutical industry. Switzerland has retained its importance for the pharmaceutical industry of today. The reasons for the strong position of Switzerland can partly be explained by successful policy-making and successful domestic pharmaceutical companies. Swiss enterprises are especially known for their smooth business transition into biology and biotechnology[93].

10.5.3 The character of technological change

In the discussion of the strategies of big pharma and national governments, it has been difficult not to mention technology. In some measure, this is due to the interrelatedness of these theoretical entities. However, it is also symptomatic of the characteristics of the R&D-intensive pharmaceutical industry: science, technology and innovation are at the core.

[92] O'Donnel, 1998, http://aei.pitt.edu/27/.
[93] Malerba & Orsenigo, 2002, pp. 667-703.

Following the discussion of key location factors for these R&D units, it can be seen that they are connected to scientific expertise and institutions. To a large extent, such factors may also explain which nations contain high concentrations of big pharma R&D units.

The discussion so far has deliberately been kept on a general level. In the next chapter, a hypothesis will be presented which will try to give a more detailed partial explanation for the distribution of big pharma R&D units.

10.6 The molecular biology revolution

Ultimately, the survival of a firm in the R&D-intensive pharmaceutical industry depends on its ability to find new drugs. Innovation within the sector was initially dependent on knowledge of chemistry. The method is usually referred to as *random screening*, involved the collection of artificial and natural compounds in large libraries. These compounds and their effect were then evaluated experimentally. When successful drug candidates had been identified, the job was to reproduce the active ingredient artificially to enable large-scale production. Indeed, large pharmaceutical companies profited from their scale and background in chemistry in the sense that they could retain large libraries of possible drug candidates and employees with experience in selecting and evaluating these compounds effectively.[94]

The publicly funded research projects that took off following the end of World War II continued during the 60s and 70s and slowly began to add to an understanding of the underlying mechanisms of pharmaceuticals. With knowledge in fields such as physiology and pharmacology, 'random screening' was slowly replaced by a new method of finding drugs. This method, called 'rational drug design', emphasised and contributed to a new understanding which would narrow down the possible compounds to choose from and so increase the efficiency of the research process.[95]

Sometime in the early 70s, universities and other publicly funded institutions made great advances in genetics. This new knowledge made it possible to produce large molecules (such as proteins) of known effect in larger quantities and assisted in the search for small molecules. Following the shift from chemistry to biology, entry barriers were broken and new players could enter the pharmaceuticals field. These firms are referred to as *biotechs* and they profited from the close relations to the universities and institutions in which the new knowledge had been produced.[96]

[94] Ibid.
[95] Ibid.
[96] Cockburn, 2005, pp. 10-22.

Despite their advantageous knowledge of biological processes over large pharmaceutical firms, biotech firms lacked the competence and resources to successfully put drugs through the approval process and out onto the market. By contrast, the large pharmaceutical companies had such abilities but lacked understanding of genetics and biology.[97]

The most commonly used strategy for big pharma was to acquire a specific competence which the company then tried to use over a broad spectrum of therapy areas. Another strategy was to build a general competence through different research collaborations with biotech firms[98]. Regardless of strategy, big pharma today is involved in both intensive collaboration and acquisitions of biopharmaceutical firms.

10.6.1 Hypothesis

The trend in the pharmaceutical industry is towards an intensification of research efforts following the 'molecular biology revolution' and the shift from 'random screening' to 'rational drug design'. These shifts are indeed shifts in both *type* and *depth* of knowledge; they are movements from chemistry and experimental practices into biotechnology and understanding of mechanisms.

On account of these shifts, places where molecular biology innovation is at the forefront (biotechnological strongholds) may be of great value for big pharma as drug development has become increasingly more scientific.

Since big pharma needs to develop drugs for its survival and the drug development process itself has increasingly come to depend on insights in molecular biology, we would expect the following changes to the spatial distribution of big pharma R&D units in Europe:

> *Recently located big pharma R&D units (in Europe) will have greater proximity toward biotechnological strongholds than historically established units.*

If this hypothesis is confirmed, there is some evidence that the increasing importance of molecular biology has had an effect on the location of big pharma R&D as long as there have not recently been other perhaps more important reasons for locating close to areas with biotechnological strongholds.

Conversely, should this hypothesis prove false there may be reasons to believe that advances in molecular biology have not had such effects in

[97] Galambos & Sturchio, 1998, pp. 250-278.
[98] Ibid., pp. 254

Europe. However, there may be other explanations too. For example historically located R&D units may be in proximity to biotechnological strongholds because there were other advantages in locating there prior to the molecular biology revolution.

10.6.2 Method

To test this hypothesis requires a definition of *biotechnological strongholds*. According to Cooke such zones, which he calls megacentres, consist of "science-driven, public and privately funded institutional complexes that in biosciences have as their ultimate goal the production of patient healthcare"[99]. Cooke identifies three such locations in Europe namely Stockholm-Uppsala, Munich and Cambridge[100]. The common characteristic is that such places have acclaimed universities in biotechnology.[101]

The Milken Institute[102] carried out a global comparison between universities and ranked them according to an index which was supposed to capture strong biotech research centres by number of publications, concentration of publications (how many publications were written within a specific subfield of biotechnology) and quality of these publications (how many times the articles had been cited). The data was collected from 683 universities of which 303 were from Europe. Publications included were published between 1998-2002. The following European universities were identified among the 50 top scoring universities:

Figure 22: Top ranked European Universities

Eurpean Top Biotech Universities

3	University of London	UK	40	University of Wales, Aberystwyth	UK
15	University of Cambridge	UK	43	Universität Basel	Switzerland
17	University of Oxford	UK	46	University of Dundee	UK
23	Universités de Paris (I-XIII)	France	48	University of Edinburgh	UK
35	Karolinska Institutet, Stockholm	Sweden	49	Universités de Strasbourg (I-III)	France
39	Université de Genève	Switzerland	50	Universität Zürich	Switzerland

Source: Milken Institute, Mind to Market: A Global Analysis of University Biotechnology Transfer and Commercialisation

It should be noted that there are essentially two problems in defining *biotech strongholds* with the above data. First and foremost, the data is connected to recent performance (1998-2002) and does not account for the status of these institutions before or after the study was undertaken. However, we shall assume that the performance during the time of measurement (1998-2002) is

[99] Cooke, 2004b, pp. 161-177.
[100] Ibid.
[101] Cooke, 2004a.
[102] DeVol et al., 2006.

linked to strong performances in the past. This assumption is based on the notion that knowledge accumulates and that research performance can usually be traced back to prior efforts[103]. Secondly, this construct rests on the assumption that big pharma research performance is highly dependent on public research and that this knowledge is best realised by locating research operations close to these centres.

To test this hypothesis empirically, we also need to assess the dynamics of the data of big pharma R&D units in Europe. There are 169 big pharma R&D units within Europe. 42 of these lack information on the date the units were taken into use. This leaves 127 R&D units with dynamic data. For the sake of this study, it will be assumed that the 42 R&D units without any dynamic information will show a similar pattern, in terms of year established and geographical location, to the 127 units with dynamic data. Naturally, leaving out roughly 25% of the total data and expecting it to 'behave' like the rest of the data has consequences for the whole study. To compensate somewhat for this 'proximity to strongholds' of the total data, the dynamic and non-dynamic data will also be presented.

According to most historical reviews, the importance of molecular biology in drug development started sometime in the 70s and was established during the 80s[104]. Although the choice is somewhat arbitrary, recent units will be regarded as 'recent' units from the 80s up until today. To add further detail to the investigation, and because it is not entirely known when or if big pharma reacted to the molecular biology revolution by means of R&D unit location/re-location, these recent units will be subdivided into 80s (for units located between 1980 and 1989), 90s (for units located between 1990 and 1999) and 00s (for units located between 2000 and 2007). All other units with dynamic data will be considered 'historical units'.

Although it is known that agglomeration externalities decrease with distance, it is difficult to appreciate the exact distance at which such externalities expire. In this study, proximity will be counted as a maximum distance of 50 km between the specific university and the R&D unit. Still, this choice of definition is a bit arbitrary, as traditionally it is mostly cities and their suburbs which have been assigned such cluster-like qualities and these can usually be encompassed within a 50 km radius[105].

[103] Dicken, 2003.
[104] Malerba & Orsenigo, 2002.
[105] Dicken, 2003, pp. 118.

10.6.3 Results

The total number of big pharma R&D units within Europe is 169. Out of these, 127 (about 75% of all units mapped) contain information on year of establishment. The countries with universities listed in the Milken Report house 83 units altogether. 59 (or about 71%) of these contain information on year of establishment.

Figure 22 below shows the percentage of R&D units (with information on year of establishment) located near any of the biotech strongholds in different time intervals. The data is presented in respect to both the countries with strongholds (France, Switzerland, Sweden, and the UK) and the European region as a whole.

Figure 23: Percentage of big pharma R&D units located near any biotechnological stronghold for "countries with strongholds" and the European region

R&D Units and Biotech Strongholds

Geographic Area	Historical	Recent		
		80s	90s	00s
Countries with Stronghold (n=59)	48%	50%	62%	86%
	(12/25)	*(3/6)*	*(8/13)*	*(13/15)*
The European Region (n=127)	24%	20%	32%	37%
	(12/49)	*(3/15)*	*8/25)*	*(13/35)*

***Explanation**: Historical refers to R&D units established prior to 1980. 80s refers to R&D units located 1980-1989, 90s refers to the period 1990-1999 and 00s refers to the period 2000-2007. The number of R&D units in proximity for that specific time period is stated (P) together with the total number of R&D units located in that time period (T) on the form (P/T) underneath each percentage.*

Of all the 169 big pharma R&D units in Europe, about 30% (52/169) are located in proximity to any of the universities highlighted in this study. Including only the countries with strongholds (France, Sweden, Switzerland and the UK) the numbers are 60% (52/83).

10.6.3.1 UK

The UK has the largest number of universities with excellence in biotechnology (6). Indeed, the UK also has the largest number of big pharma R&D units (39) in Europe. Out of these units, largest 31 include information on the year of establishment; ten were established before the 80s, three during the 80s, eight during the 90s and ten have established so far this century.

Figure 23 shows the percentage of these R&D units in different time frames (Historical, 80s, 90s and 00s) that are located in proximity to a specific university. The figure also includes 'Proximity to Strongholds' which is an

aggregate of the percentage of R&D units located close to any of the universities included.

Figure 24: Big pharma R&D units location in reference to biotechnological strongholds over time (in the UK)

R&D Units and Proximity to Biotech Strongholds (UK)

R	University	Historical	Recent 80s	90s	00s
		(10U)	*(3U)*	*(8U)*	*(10U)*
3	University of London	40%	66,6%	50%	70%
15	University of Cambridge	n/a	n/a	37,5%	30%
17	University of Oxford	10%	10%	n/a	n/a
40	University of Wales, Aberystwyth	n/a	n/a	n/a	n/a
46	University of Dundee	n/a	n/a	n/a	n/a
48	University of Edinburgh	n/a	n/a	n/a	n/a
	Proximity to Strongholds	**50%**	**66,6%**	**87,5%**	**100%**

Explanation: *R stands for the global ranking of the university in the Milken Report. Historical refers to R&D units established prior to 1980. 80s refers to R&D units located 1980-1989, 90s refers to the period 1990-1999 and 00s refers to the period 2000-2007. The total number of units located within the country during a certain time-frame is included in brackets. The percentage given for a specific time (such as Historical) and a specific university (London for example) is denoted by the number of R&D units located in proximity to that specific university, divided by the total number of R&D units located in the country within that timeframe. Universities that lack R&D units in proximity within a specific timeframe have been assigned n/a. Whenever two or more universities are in proximity to an R&D unit, the closest university will be accounted for the unit.*

Thus, for all big pharma R&D units located within the UK; 49% (19/39) are located near the University of London, 18% (7/39) are near the University of Cambridge and 8% (3/39) are near the University of Oxford. None of the other universities have R&D units in proximity.

10.6.3.2 France

France has two universities with excellence in biotechnology. A total of 29 R&D units are located in France (including one in Monaco). Of these, only slightly more than half the units (16) have dynamic data assigned to them. Eight of these units were located historically, two during the 80s, one during the 90s and four since 2000. As with figure 23, the figure below summarises proximity to strongholds within France:

Figure 25: Big pharma R&D units location in reference to biotechnological strongholds over time (in France)

R&D Units and Proximity to Biotech Strongholds (France)

R	University	Historical	Recent 80s	90s	00s
		(8U)	*(2U)*	*(3U)*	*(4U)*
23	Universités de Paris (I-XIII)	25%	50%	n/a	75%
49	Universités de Strasbourg (I-III)	n/a	n/a	n/a	n/a
	Proximity to Strongholds	**25%**	**50%**	**n/a**	**75%**

***Explanation**: For further information see explanation of figure 23.*

Currently, of all the 29 R&D units in France 45% (13/29) are located close to Universités de Paris (I - XIII) whereas only 3% (1/29) lie in proximity to Universités de Strasbourg (I - III).

10.6.3.3 Switzerland

Switzerland has three universities with recognised academic achievements in biotech. A total of 11 R&D units are located in Switzerland. The year of establishment has been determined for eight of these units. Four of these units were located historically, three were established during the 90s and one in 2003.

Figure 26: Big pharma R&D units location in reference to biotechnological strongholds over time (in Switzerland)

R&D Units and Proximity to Biotech Strongholds (Switzerland)

R	University	Historical	Recent 80s	90s	00s
		(4U)	*(0U)*	*(3U)*	*(1U)*
39	Université de Genève	n/a	n/a	33%	n/a
43	Universität Basel	50%	n/a	n/a	n/a
50	Universität Zürich	50%	n/a	n/a	n/a
	Proximity to Strongholds	**100%**	**n/a**	**33%**	**n/a**

***Explanation**: For further information see explanation of figure 23.*

Out of the 11 big pharma R&D units in Switzerland, 27% (3/11) are located in proximity to Université de Genève and 27% (3/11) to Universität Basel whereas 18% (2/11) are close to Universität Zürich.

10.6.3.4 Sweden

In Sweden, Karolinska Institutet is the top university according to the Milken Report. There are four big pharma R&D sites in Sweden of which

three were located historically and one in the 80s. There are no locations with unknown year of establishment.

Figure 27: Big pharma R&D units location in reference to biotechnological strongholds over time (in Sweden)

R&D Units and Proximity to Biotech Strongholds (Sweden)

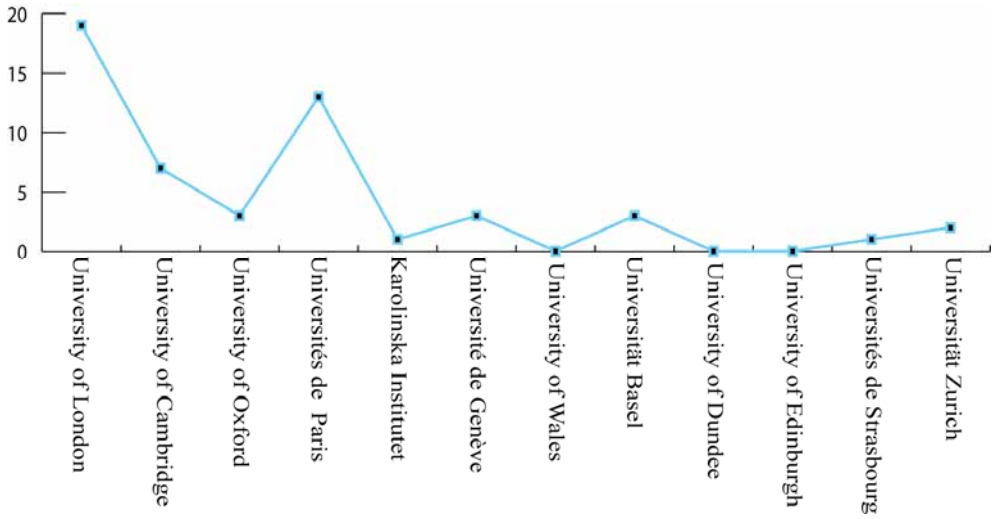
R	University	Historical	Recent		
			80s	90s	00s
		(3U)	*(1U)*	*(0U)*	*(0U)*
35	Karolinska Institutet	33%	n/a	n/a	n/a

***Explanation**: For further information see explanation of figure 23.*

10.6.3.5 The universities

Figure 27 below shows the number of big pharma R&D units in proximity to each of the universities aligned according to the global ranking assigned to them[106].

Figure 28: The number of big pharma R&D units in proximity to each of the biotech strongholds.



10.6.4 Discussion and analysis

The results show some evidence of an increasing fraction of big pharma R&D units in Europe being located in proximity to biotechnological strongholds. However, these trends are mostly accounted for within France and the UK. No such trend can be seen in Switzerland and Sweden. On an aggregate level, the trend is greatest between the 90s and 00s for countries with strongholds.

[106] DeVol et al., 2006.

The general proximity toward strongholds, including all of the data, show strongest concentrations within the UK and Switzerland (about 75%) whereas France (50%) and Sweden (25%) have fewer R&D units in proximity to strongholds.

Furthermore, the location of big pharma shows a higher affinity toward the highly ranked universities in each of the countries considered. Indeed, most R&D units located in the UK are solely accounted for by the universities of Oxford, Cambridge and London. The three universities in UK with lower ranking do not have any big pharma R&D units located in proximity. In France, Universités de Paris (I - XIII) have much higher concentrations than Universités de Strasbourg (I - III). The Swiss universities are much more equal in terms of number of R&D units in proximity. Overall, it seems big pharma is drawn to big universities.

As mentioned before, Cooke argues that industry concentration is increasing and that these places, the megacentres, are the leading innovative force within the pharmaceutical industry. There is some overlap between the universities considered in this study and Cooke's megacentres of Europe. These regions are the Cambridge region, home to Cambridge University and close to London and Oxford University, as well as the Stockholm-Uppsala region which houses Karolinska Institutet. Although there are many similarities between these regions in terms of number of biotechnology firms and number of researchers, the results presented in this paper show striking differences in the presence of big pharma R&D units[107]. Cooke gives no satisfactory answer to these differences but in general he proclaims:

> *Moreover, the traditional pharmaceuticals industry ('pharma') is seen to be moving its 'knowledge production' into what are becoming 'bioscience megacentres' rather than simply 'business clusters' by new openings and acquisitions, but mainly by bankrolling 'dedicated biotechnology firms' (DBFs).*[108]

If this is true, the explanation for the differences in big pharma R&D presence in the two regions (Cambridge and Stockholm-Uppsala) could lie in the way in which the 'moving in' to these regions has been facilitated. In the case of Cambridge, as we have seen, the movement consisted of new openings. In Stockholm-Uppsala, the movement, which may have been by means of undertakings and collaborations, is not visible in our results.

[107] The third megacentre in Europe (Munich) was not included in this study but has only three big pharma R&D units located there.
[108] Cooke, 2004b, pp.162.

Figure 29: Regional Biotech Comparison

Regional Biotech Comparison

Location	DBFs*	Number of life scientist	Venture Capital *($ million)*	Big Pharma funding *($ million)*
Boston	141	4980	601.5	800 per annum 1996-2001
San Fransisco & Silicon Valley	152	3090	1063.5	400 per annum 1996-2001
San Diego	94	1430	432.8	320 per annum 1996-2001
Toronto	73	1149	120.0	n/a
Montreal	72	822	60.0	n/a
Munich	120	12000	400.0	54 (2001)
Stockholm & Uppsala	60	2998	100.0	n/a
Cambridge (UK)	54	2650	250.0	105 (2000)

* DBF = Dedicated Biotechnology Firm

(Source: P Cooke, The molecular biology revolution and the rise of bioscience megacentres in North America and Europe

10.6.4.1 What about the other R&D units?

This study has shown that there is some trend toward location of big pharma R&D near biotechnological strongholds; however, this trend is far from firm and conclusive. What about all the other big pharma R&D units scattered across Europe? What could be the reasons for maintaining these?

The strong tendency toward R&D location in proximity to acclaimed universities is, as in the case of the UK and France, strongest when the university is embedded in a large city. Indeed, the five largest agglomerations of big pharma R&D units are near London, Paris, Brussels, Madrid and Amsterdam (see figure 29).

Figure 30: Agglomerations defined within a circle of radius 50 km

Agglomeration

Location	Size of Agglomeration *(Number of R&D Units)*
London/Cambridge	23
Paris/Ile de France	13
Brussels area	8
Madrid	8
Amsterdam	6
Copenhagen	5
Frankfurt	5
Milan	4
Munich	3
Basel	3
Cork	3
Oss	3
Rome	3
Vienna	3

The existence of these agglomerations suggests that some location factors, apart from the existence of scientific competence and institutions, are specifically linked to some of the characteristics of large cities. These may indeed be 'trivial' factors connected to infrastructure and living standards.

One other explanation for the scattered geography of big pharma R&D units in Europe may be the fact that drug design is not all about biological applications but still has some base in knowledge from chemistry. Indeed, over half of the drugs approved in 2003 were chemical entities.

Furthermore and as already mentioned[109], location should be understood to a considerable degree in terms of path-dependency: Naturally, a lot of effort is needed to make R&D investments at a completely 'new site' rather than to invest in familiar territory. There are sometimes also conflicting needs at stake, such as the need for control which would make it more reasonable to retain R&D in proximity to headquarters located at 'old' industrial hotspots.

10.6.5 Evaluation

There have been several problems in finding a suitable method for this hypothesis. Biotech strongholds were defined by ranking universities with excellence in biotechnology because this is a key characteristic of regions with strong pharmaceutical innovation capacities. However, it is not the only ingredient and thus a better selection of pharmaceutical strongholds would include also other factors. Furthermore, it is largely unclear whether big pharma gains from any of the externalities in these milieus by means of locating R&D units there. Moreover, the data on the selected universities was only based on recent performance.

Another big problem has been the limited information on dynamics. Indeed, the 42 R&D units without any information on the year of establishment have the 'power' to disqualify some of the trends seen. Furthermore, these R&D units only capture some of the business activity of big pharma. As the pharmaceutical industry seems to be moving more extensively into a network structure, one must question the share of big pharma R&D activity actually being 'mapped'. In further studies, it would be important to take account of this network character perhaps by making extensive mappings of just a few companies and their linkages. However, due to the complexity, size and discretion in some of the network linkages, such a complete mapping would be difficult to accomplish.

[109] Hayter, 1997.

10.7 Conclusions

The big pharma R&D geography in Europe is difficult to explain fully. Every single location is the result of a unique event for a certain company subjected to various inner and outer constraints. On an aggregate level, the location of R&D units seems to follow the influences of TNCs, nations and technology. However, such trends are difficult to isolate due to the low number of locations and absence of any appreciation of the size of these units.

In this chapter, the molecular biology revolution has been shown to have some influence on the location of big pharma R&D units. However, this trend is not convincing and as innovation is at the core of the industry some[110] are questioning the future of the big pharma business model. Possibly in the future, big pharma would need to adjust more keenly than it has done so far. Naturally, such adjustments would have tremendous effects on the geography of big pharma R&D in Europe. These possible future changes will be discussed in more detail the end of this paper.

[110] See for example Gilbert, Henske & Singh (2003).

11 Clusters[Ω]

This case study benchmarks four clusters environments[111], namely: Massachusetts, Ireland, Singapore, and Switzerland. The clusters were selected on the basis of the high concentrations of companies found in our empirical data and also because they are primary competitive regions to Sweden in the life science industry. According to Porter's theory, presented in section 6.3, there are factors that are necessary inputs for clusters to be competitive in industries, such as the life science industry. Therefore, the paper first describes the policy of each cluster (e.g. federal government funding, venture capital investment, tax costs, and infrastructure). These factors are some of the inputs needed for understanding the competitive position of companies in each cluster, since the life science industry is dependent on research funding and a stable environment. The business climate of each cluster is then described, with a focus on the life science industry. The business climate of each cluster is based on biological knowledge and research, academia, and innovation milieus. These are advanced factors that can be changed, created or removed (also mentioned in the theory section) and are significant to competitive advantage. A comparison of the four clusters will ultimately be conducted, indicating differences and similarities between the clusters.

11.1 Massachusetts

11.1.1 History

The creation of Massachusetts life science was cluster-initiated with the founding of Harvard University in 1636 and the Massachusetts Institute of Technology (MIT) in 1861. They were located on each side of the Charles River, Harvard University at Kendall Square in Cambridge and MIT at Longwood Medical Area (LMA) in Boston[112]. LMA is an area with a high density of hospitals and colleges, while Kendall Square is more famous for its numerous laboratories and discoveries of biotechnology and pharmaceuticals. Still, the two centres are less than three miles apart. Since many of the biopharmaceutical discoveries were coming out of academia it was normal that the industry should first be established in areas near to universities and research hospitals[113]. In the early 20th Century, Harvard

[111] Cluster environment and cluster milieu will be used interchangeably.
[112] *Massachusetts BioHistory*, http://www.massachusettslifescience.com/biohistory.htm.
[113] Massachusetts Biotechnology Council, 2006.

University sold some of its properties on Longwood Area to other hospitals so that Harvard students could benefit from the collaboration. Meanwhile, MIT moved its campus to Kendall Square, bringing about this cluster[114].

11.1.2 Life science policy in Massachusetts

11.1.2.1 NIH grants to Massachusetts

Today, pharmaceutical innovators in Massachusetts attract an enormous amount of funding for research that leads to growth in the life science cluster. The federal government supports over 35% of all R&D in Massachusetts: it maintains continued development and expansion of existing clusters[115]. Several federal agencies provide funding for Massachusetts R&D, one of the most important sources of this funding being the National Institute of Health (NIH), located within the Department of Health and Human Services (HHS). In fiscal year (FY) 2005, NIH awarded Massachusetts USD 2.27 billion in funding, which is almost 10% of the total US grant. The largest segment of the NIH budget is dedicated to research project grants, in FY 2005, NIH allocated 90% of the total funding to research projects[116].

Figure 31: Top NIH grantee states FY 2005

NIH grantee states

	Research Grants ($ billions)	as percentage of total NIH grants	per capita
1. California	3.30	16.6%	$91
2. Massachusetts	2.27	11.4%	$353
3. New York	2.02	10.1%	$105
4. Maryland	1.76	8.8%	$316
5. Pennsylvania	1.45	7.3%	$117
Total (US) NIH Research grants	19.9	100%	$67

Source: http://officeofbudget.od.nih.gov/UI/.%5CFY05%5CMechanismTotal.pdf

[114] Pricewaterhousecoopers, 2007, http://www.masstech.org/institute/life_science/supercluster.pdf.
[115] The R&D Funding Scorecard: *Federal Investments and the Massachusetts Innovation Economy*, 2003, http://www.masstech.org/institute/the_index/index_2003.pdf.
[116] Pricewaterhousecoopers, 2007, http://www.masstech.org/institute/life_science/supercluster.pdf.

Even though California received the highest dollar amount of NIH funding, Massachusetts received the most NIH funds per biopharmaceutical worker of any state in the nation, with USD 353 per capita[117].

11.1.2.2 Grant recipients

Massachusetts' NIH funding is distributed among institutions, hospitals and research organisations. Massachusetts General Hospital was the number one recipient among all institutions in the state with USD 287 million in R&D support, followed by Brigham and Women's Hospital with USD 253 million in funding. Among the colleges and universities, Massachusetts Institute of Technology (MIT) topped the list, total at number three, with USD 172 million, followed by Harvard University Medical School with USD 169 million[118].

The organisations in the Massachusetts pharmaceutical cluster depend on funding from the federal government and private investment. Since the budget for NIH funding has levelled off after doubling during 1998-2003, the competition for NIH funding is fierce[119]. If the decline in funding continues, it could have a serious impact on the Massachusetts research funding. For the Medical Institutions in the Boston area that provide work for over 150,000 people and add over USD 24 billion to the state economy annually[120], it is clear that the stakes are high.

11.1.2.3 SBIR and STTR NIH grants

The Massachusetts life science clusters receive important funding from NIH that provides a foundation for biomedical research. The life science cluster also profits from two grant programmes, coordinated by the Small Business Administration (SBA), in which a part of the extramural research budgets of government agencies are reserved for grants to small businesses employing less than 500 people[121]. The Small Business Innovation Research (SBIR) programme requires agencies with annual extramural research and development budgets higher than USD 100 million to reserve at least 2.5% for awards to small technology companies. The Small Business Technology Transfer Research programme (STTR) qualifications are that the budget for agencies with annual extramural research must exceed USD 1 billion,

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[117] Ibid.
[118] Ibid.
[119] Ibid.
[120] Roland, 2007. http://www.boston.com/business/healthcare/articles/2007/03/06/funding_slowdown_worries_hospitals/
[121] Handbook for SBIR Proposal Preparation 2007, http://www.sba.gov/gopher/Innovation-And-Research/SBIR-Pro-Prep/ 071106.

setting aside 0.3% for small US high-tech firms[122]. As shown in figure 31, Massachusetts received over USD 84 million in financial support through SBIR and STTR programmes in 2005.

Figure 32: SBIR and STTR grants to Massachusetts, FY 2005

NIH SBIR and STTR grants to Massachusetts

	Number of grants	Total amounts ($ millions)
SBIR		
Phase 1 - start up phase	114	21.5
Phase 2 - expand phase 1 results	110	53.3
Total SBIR	224	74.5
STTR		
Phase 1 - start up phase	20	3.9
Phase 2 - expand phase 1 results	10	5.6
Total STTR	30	9.5
Total SBIR & STTR	**254**	**84.3**

Source: National Institute of Health, Office of Extramural Research

11.1.3 Venture capital

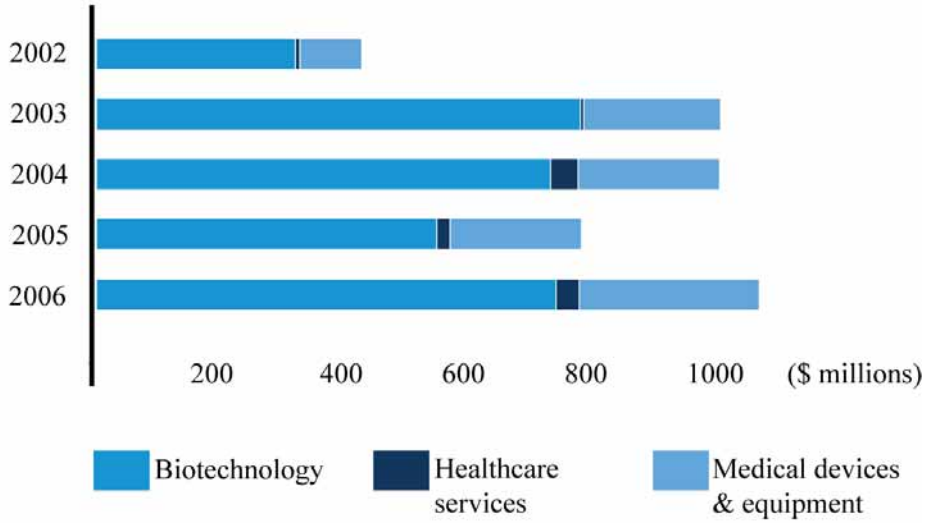
Biomedical research requires large amounts of capital, which comes from investors that understand the science and risks associated with it. Venture capitalists are one group that meets these criteria; in 2006, they provided USD 1.1 billion in financial support to Massachusetts life sciences and health industries companies, a 43% raise over the previous year. Almost two-thirds (USD 755 million) of the funding went to the biotechnology segment with firms focusing on cancer, autoimmune diseases and diabetes. The remainder went to medical devices and equipment companies[123]. The total volume of biotechnology venture capital invested in firms by state is an indicator of how investors view the state as location for biotechnology companies.

Massachusetts was second overall in receiving total venture capital financing companies, behind California. But the increase of 43% in venture investments in 2006 exceeded the 10% growth rate for California. In

[122] Pricewaterhousecoopers, 2007, http://www.masstech.org/institute/life_science/supercluster.pdf.
[123] Venture Capital investment in Health Industries Report: *New England Health Industries Full-Year 2006 Results, the MoneyTree Report from PricewaterhouseCoopers and the National Venture Capital Association based on data provided by Thomson Financial* 2007, https://www.pwcmoneytree.com/MTPublic/ns/moneytree/filesource/exhibits/MoneyTree_NE_HealthIndustriesReport_FY2006.pdf.

general, venture capital investment between 2002 and 2006 more than doubled in Massachusetts[124].

Figure 33: Venture Capital investment in Healthcare Industries 2006



Source: PricewaterhouseCoopers and the National Venture Capital Association. Venture Capital investment in Health Industries Full Year 2006 Report, the MoneyTree Report

11.1.4 Tax cost

At 9.5%, the corporate tax rate in Massachusetts is one of the highest among US states.[125] But the *Single Sales Factor (SSF)* method of tax distribution has significantly reduced the firms' state tax that lead to Massachusetts becoming the most competitive state in terms of state tax weight[126]. In addition to this there is also a federal corporate tax, which varies between 15% and 39% depending on company revenues.[127]

Until 1996, Massachusetts corporations were taxed on the basis of three factors in their operations:

1 Percentage of sales arising in the state.
2 Percentage of payroll located in the state.
3 Percentage of property located in the state.

[124] PricewaterhouseCoopers & the National Venture Capital Association. 2006, http://www.pwc.com/extweb/pwcpublications.nsf/docid/CEB57559F1D0AF1D8525728F0004D828.
[125] MassDevelopment & the Massachusetts Alliance for Economic Development, 2003,http://www.biotechwork.org/pages/FileStream.aspx?mode=Stream&fileId=5cd27f43-4cf4-db11-b900-00c09f26cd10
[126] 'Corporate Tax Breaks Approved', 1995, pp. 45.
[127] *Publication 542: Corporations*, http://www.irs.gov/pub/irs-pdf/p542.pdf.

In response to worries about the high costs doing business in Massachusetts, the SSF method was introduced for the defence industry and other manufacturing industries[128]. For the manufacturing industry, the SSF method only takes into account the percentage of sales arising in the state in order to determine income declared to Massachusetts. It does not consider the property location or payroll. To illustrate: your company sells products in all US states. You have half the payroll and 40% of the property in Massachusetts since the majority of the facilities and your head office are located here. Assume 2% of the products are sold in Massachusetts, and the annual profits amount to USD 10 million. Before SSF was adopted in Massachusetts, the state corporate income tax would be:

USD 10,000,000 x (0.5 (payroll) + 0.4 (property) + 0.02 (sales)/ 3) = USD 3,066,667

About USD 3.07 million of company income would be shared with Massachusetts for tax purposes. But after SSF was adopted for manufacturers, only the sales factor determines the tax, so the calculation looks like this:

USD 10,000,000 x 0.02 (sales) = USD 200,000

This makes Massachusetts a more competitive location for firms with a lot of workers and major capital investment[129].

11.1.5 Infrastructure

Massachusetts lacks a transportation strategy and since it is one of the most urbanised states in the country. More than 87% of state citizens live within an urbanised area and own more cars per individual than the national average. Thus, Massachusetts faces many challenges in meeting its transportation requirements. One of these is aging infrastructure. Massachusetts has over 5,000 bridges of which half are structurally inadequate. Furthermore, almost 30% of the highways are in poor condition[130]. Another challenge is the extremely busy Logan International Airport. This Airport is an important centre for processing domestic and

[128] Merkowitz, 2004, http://www.taxadmin.org/FTA/meet/re_pres04/merkowitz.pdf.
[129] MassDevelopment and the Massachusetts Alliance for Economic Development, http://www.biotech work.org/pages/FileStream.aspx?mode=Stream&fileId=5cd27f43-4cf4-db11-b900-00c09f26cd10.
[130] Associated Industries of Massachusetts, 2002, http://www.massinsight.com/docs/Transition2002_TelecomBrief.PDF.

international air cargo; it is also important for business and personal travellers and since delays are common it can cause problems[131].

11.1.6 Business climate

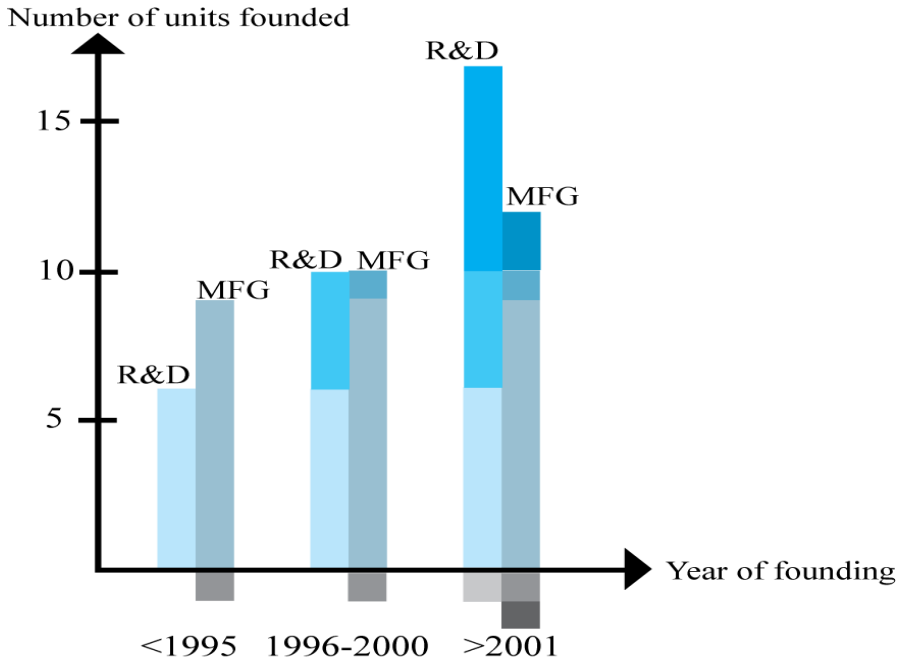
Massachusetts has established itself as a centre of bio-pharmaceutical research and product development. To quantify the presence of big pharma in Massachusetts, estimates are made by the identification and mapping of the big pharma companies for which data has been analysed.

A total of 20 big pharma companies are located in Massachusetts, with 22 R&D units, 13 manufacturing units, and two headquarters. Notable pharmaceutical companies in Massachusetts, include Pfizer, Wyeth, AstraZeneca, Novartis, Bristol-Myers Squibb, Genzyme, Amgen, and Merck. For the entire country, there are 147 R&D units, 159 manufacturing units, and 20 big pharma headquarters. Of the total R&D and manufacturing units in the US, 10% are located in Massachusetts according to the empirical data compiled. Big pharma in Massachusetts is focusing strongly in neuroscience, oncology, and technologies in order to develop new medicines[132]. In addition, many smaller companies are located in the state and acting alone or in alliance with the larger companies in the development of new drugs.

The accumulation diagram in figure 34 shows the establishment of big pharma companies in Massachusetts over time. Since not all founding years are available in our empirical data, this diagram covers a total of 17 R&D units and 12 manufacturing units in Massachusetts. During the time schedule shown in the figure, only one R&D unit and two manufacturing units have closed in Massachusetts. The different colours represent the periods during which the unit was established or closed, and are shown as an accumulation so as to provide a view of the total number of units. Similar diagrams with the same properties will be shown for the remaining three clusters described in this chapter.

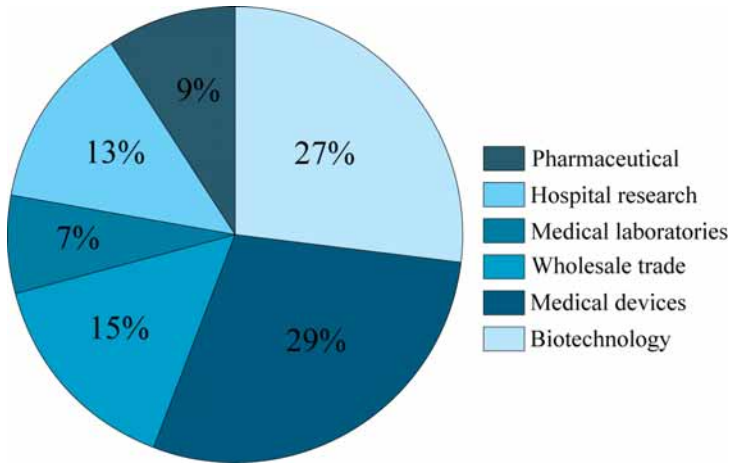
[131] *The Boston Indicators Project*, http://bostonindicators.org/indicatorsproject/transportation/indicator.aspx?id=1962.
[132] *Cambridge: The Brains of Biotech, the Heart of Innovation,* http://www.ci.cambridge.ma.us/CDD/ed/pubs/ed_biotech_broch.pdf.

Figure 34: Units in Massachusetts



In the life science industry as of 2005, there were 74,100 people working in six core segments. These include the pharmaceutical with 6,900 employees, biotechnology with 19,700 employees, medical devices with 22,000 staff members, wholesale trade with 11,000 workers, medical laboratories with 5,000 workers, and hospital research with 9,300 employees. The distribution is shown in figure 35.[133]

Figure 35: Employment in the healthcare industry in Massachusetts



Source: Bureau of Labor Statistics Quarterly Census of Employment and Wages, and PricewaterhouseCoopers analysis

[133] Pricewaterhousecoopers, 2007, http://www.masstech.org/institute/life_science/supercluster.pdf.

Within the state, major pharmaceutical and biotechnology firms are concentrated in the metropolitan Boston region. A natural explanation for this may be that the leading universities are concentrated in this area. The highly skilled Massachusetts workforce is the product of a strong educational structure. In 2003, the state had the highest percentage of employees with a Bachelor's degree or higher. The focus on educated workforce has resulted in the development of world-leading medical research, and consequently a number of Nobel Laureates from the universities of Massachusetts[134].

11.1.6.1 Boston-Cambridge

There are five development districts in Cambridge: Concord/Alewife, Lower Cambridge port, University Park, Kendall Square, and North Point, of which only two of these will be described here because the majority of pharmaceutical companies are located there.

The Concord/Alewife area is one of the largest areas of Cambridge with major development potential. There is 51,000 m² of R&D utilisation, most of which is located in the subdistrict of Little site. Other sub districts are the Triangle area along Cambridge Park Drive that contains 158,000 m² of office/R&D places, and Quadrangle with 185,800 m² of industrial companies, such as pharmaceutical and technology firms located here[135].

The Kendall Square area, home to MIT, is the major locus for life science activity and R&D. It has become the anchor of the Cambridge cluster of biotech and pharmaceutical companies, which includes Cambridge Centre, Cambridge Research Park and Technology Square. The Cambridge Centre has 251,000 m² space for R&D/laboratory facilities, the Technology Square (owned by MIT) provides 149,000 m² of office space, and Cambridge Research Park covers 40,000 m² of office and lab space. As mentioned in the cluster theory, the benefits of industry clusters include good access to customers, scientific exchange between cluster companies, and a skilled workforce. These advantages are most in evidence for the cluster around Kendall Square, due to the concentration of the companies and Universities/Institutions[136].

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[134] Sum et al, 2006, http://www.massinc.org/fileadmin/researchreports/labor_supply/labor_supply_full.pdf .
[135] *Concord-Alewife Rezoning Petition,* 2006, http://www.cambridgema.gov/cdd/cp/zng/concalew/conale_guidelines.pdf.
[136] *City of Cambridge,* 2004, http://www.cambridgema.gov/~CDD/ed/pubs/ed_policy_2004.pdf.

11.1.7 Academia

Massachusetts academic and research institutions are playing a central role in the creation of cluster growth. Cambridge has several of the most prominent universities in the world, including Harvard University, ranked as number one among all universities in the world according to the Academic Ranking of World Universities 2007 and Massachusetts Institution of Technology (MIT) rated behind Harvard at number four in the world[137]. In 2006-2007 these had student populations(undergraduate and graduate enrolments) of 20,042[138] and 10,253[139] respectively.

11.1.7.1 Harvard and MIT

Harvard and MIT collaborate to integrate science, engineering, and medicine in exploring the principles underlying health and disease, including the search for new pharmaceuticals and devices. One of the educational programmes is the Harvard-MIT Division of Health Sciences and Technology (HST), which has three major research focus areas; biomedical imaging, bioinformatics and integrative biology, and biomedical technology[140].

Many of the academic institutions in the cluster focus on identifying and developing cancer treatments. One of these faculties is the MIT-Harvard Center of Cancer Nanotechnology Excellence (CCNE); it is a collaboration between MIT, Harvard University, Massachusetts General Hospital, and Brigham Hospital. The centre is one of seven national, multi-institutional hubs supported by the National Cancer Institute (NCI), part of the NIH. The goal of this centre is to advance the aims of nanotechnologies in cancer research[141].

11.1.7.2 Other research centres

The Whitehead Institute is a leading, non-profit independent research institution with programmes in cancer research, genetics and genomics. The research is conducted by approximately 20 researchers and over 200 visiting scientists from around the world. Whitehead is connected to the MIT in its education activities, but totally responsible for its own research

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[137] Shanghai Jiao Tong University, 2007 http://ed.sjtu.edu.cn/rank/2007/ARWU2007.xls .
[138] *Harvard Fact Book*, 2007, http://vpf - web.harvard.edu/budget/factbook/current_facts/2007OnlineFactbook.pdf
[139] *MIT facts,* 2007, http://web.mit.edu/facts/enrollment.html .
[140] *HST Research Focus Areas*, http://hst.harvard.edu/servlet/ControllerServlet?handler=PublicHandler&action=browse&pageId=831 .
[141] MIT Center for Cancer Research, http://web.mit.edu/ccr/about/MIT%20CCR%20FAQs.pdf.

programmes, and financing[142]. The institute has an annual budget of USD 46 million; approximately half of the financing comes from research grants awarded by the federal government, whereas 41% of the funds go directly to sponsored research and 21% go to central administration[143].

The Broad Institute is a research collaboration between MIT and Harvard, its associated hospitals and the Whitehead Institute, but is governed by MIT and Harvard University. Its purpose is to develop the potential of genomics for medicine[144]. According to MIT's newsletter in November 30, 2005, 18 months after the opening of the institute in 2004, Los Angeles residents and philanthropists Eli and Edythe Broad, donated USD 200 million to the Broad Institute. The first donation was a USD 100 million gift to MIT with the other USD 100 million donation going through Harvard. The combined donation will span a 10-year period, given as USD 20 million per year.

McGovern Institute was established in 2000 at MIT, when Pat and Lore McGovern donated the largest gift ever to MIT of USD 350 million. It is a neuroscience research institute focusing on brain disorders, with 11 researchers conducting neuroscienctific research in three areas; perception, cognition, and action. [145]

Close to the McGovern Institute for Brain Research, the Picower Center for Learning and Memory and Department of Brain and Cognitive Sciences have built a new complex which opened in 2005. Located at MIT, it will house over 40 faculties and their research groups. The mission of this complex is to be the largest neuroscience research centre in the world. It offers undergraduate and graduate students a high quality educational experience and supplies students to participate in research projects with leaders in their fields[146].

The collaboration with academic researchers has many uses, such as; creating intellectual properties, testing theories in practice, and collaborating on clinical trials. Therefore, collaboration with Massachusetts universities is of importance for the industry.

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[142] Whitehead Institute for Biomedical Research, http://www.wi.mit.edu/about/index.html.
[143] Whitehead Institute for Biomedical Research, http://www.wi.mit.edu/about/2006_annualrpt.pdf.
[144] Broad Institute, http://www.broad.mit.edu/about/index.html.
[145] McGovern Institute for Brain Research at MIT, http://web.mit.edu/MCGOVERN/html/Who_We_Are/facts_at_a_glance.shtml.
[146] MIT's Department of Brain and Cognitive Sciences, http://web.mit.edu/bcs/aboutbcs/.

11.1.8 Innovation milieus

Cambridge Innovation Center (CIC) is located in the heart of Kendall Square next to MIT campus and has the largest office facility for small and growing technology companies in the Boston area. The CIC instantly provides secure, furnished work spaces (including R&D) which are cost effective for minor companies, free job advertising, and technical services for companies to become successful in the Cambridge cluster. The residents at CIC are often growing technology firms, venture capital firms, patent agents, and service companies; today over 150 companies are located in CIC[147].

The Deshpande Center was established in 2002 as a part of the MIT School of Engineering, through an initial USD 20 million donation from Jaishree Deshpande and Desh Deshpande; it supports innovation and entrepreneurship by enhancing MIT research and the impact of MIT technologies in the market. Since its establishment, the centre has funded 64 projects with over USD 7 million in grants. The Centre supports a wide range of emerging technologies including biotechnology, medical devices, and environmental innovation etc[148].

McGovern Institute Neurotechnology (MINT) Program was created in 2006 to support collaborations between neuroscientists and researchers within and outside MIT with an objective of technical innovation that will help develop new technologies for brain research. The founding donors of the McGovern Institute, Patrick and Lore McGovern provided funding for projects that will lead to development of new tools for neuroscience research[149].

11.1.9 University technology transfer

New inventions and patents are becoming a more important feature in technology licences offered by universities. Many universities have a goal of putting research results to good use. A technology transfer programme has thus developed so that basic science and research developments get out to the public more efficiently. The act allows universities to name inventions arising from their research and licence these technologies to companies wishing to take them to market[150]. There are two offices at Harvard University and MIT using this type of programme: OTD and ILP.

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[147] Cambridge Innovation Center, http://www.cambridgeincubator.com/.
[148] Desphande Center for Technological Innovation, http://web.mit.edu/deshpandecenter/about.html
[149] McGovern Institute for Brain Research at MIT, http://web.mit.edu/mcgovern/html/Areas_of_Research/mint.shtml.
[150] The Association of University Technology Managers, http://www.autm.net/aboutTT/.

Office of technology development (OTD) at Harvard University has a mission to make the research at Harvard more accessible outside the University, and let the community benefit from Harvard innovations by converting their research capacity into commercial activity. OTD's goals are to commercialise Harvard research discoveries for public use, promote economic growth by serving as a bridge from laboratory to industry, translate new technologies into products that will be available to society, and patent and licence discoveries and inventions made at Harvard University. Companies may seek to licence discoveries made at Harvard to be able to develop products, such as pharmaceuticals. Technology transfer is a way of licensing intellectual property results from the Harvard research[151]. OTD grants licences to both existing and new companies, in either case OTD ensure that the industry partners own the financial resources and technical competence, to develop successful products. To further its mission and to be able to grant licences, OTD has established the Harvard University Technology Development Accelerator Fund. The purpose of the "Accelerator" programme is to overcome what is known as the *development gap*, since very promising new inventions are often at an early stage of development and, due to lack of financial support, many new technologies with potential never make it out of the lab[152].

Industrial Liaison Program (ILP) was established in 1948 at MIT to act as a link between university and industry. ILP joins member companies with the latest research developments at MIT whilst helping industry support MIT's research output. A large number of companies, approximately 200 worldwide, turn to ILP for access to professional MIT researchers and information that will help them bring innovation to market[153]. Each company joining ILP is assigned an Industrial Liaison Officer (ILO) who knows the industry and can rapidly grasp the important emerging MIT technology and help the company develop ways to influence it for commercial advantage. The ILO is positioned to be an effective supporter for the needs of companies, and understand what they want to achieve at MIT. The minimum annual fee to become an MIT ILP member, is USD 60,000, and the company must commit to a two-year membership[154].

[151] Harvard University Office of Technology Development, http://otd.harvard.edu/about/.
[152] Harvard University Office of Technology Development, http://otd.harvard.edu/inventions/acceleratorfund/.
[153] Office of Corporate Relations and the Industrial Liaison Program, http://ilp-www.mit.edu/display_page.a4d?key=P2.
[154] Ibid.

11.2 Ireland

11.2.1 History of the life science sector

In the late 1950s, the Irish economy was dependent on agricultural products, fishing, and forestry that accounted for a large proportion of jobs and exports; there was virtually no pharmaceutical industry in Ireland. During the late 20th Century, the government decided to invest in knowledge-based industries, such as chemical, pharmaceuticals, and electronics through a combination of grant and tax incentives that would attract many companies to Ireland. The country also invested heavily in the educational system to ensure access to a skilled work force that could work in the new high-tech firms[155]. Through the work of the Industrial Development Authority (IDA) in the 1970s, the pharmaceutical industry expanded. The attraction of foreign companies and employment also grew markedly, from 1,300 in 1972 to 4,750 in 1979 in the pharmaceutical sector. During the 1980s, pharmaceutical companies in Ireland focused on manufacturing. The growth of life science led to the expansion of existing firms and attraction of new companies[156].

11.2.2 Life science policy in Ireland

The major programmes involved in the foundation of life science in Ireland are SFIs, and the HEA programme. Both of these initiatives have the aim of leading to rapid progress in establishing world-class research in Ireland.

11.2.2.1 Higher Education Authority (HEA)

HEA started in 1968 and is the authority in Ireland with responsibility for higher education and research. HEA has advisory and funding functions for the universities and higher education institutions, since this sector plays a central role to national innovation. Some of the universities funded by HEA are University College Cork, University College Dublin, and National University of Ireland. Research programmes funded by the HEA support collaboration between institutions and between research disciplines for the benefit of Ireland. The range of HEA funding activities in the research system is:

- Providing necessary grants for research funding
- The Programme for Research in Third-Level Institutions (PRTLI) supports large research programmes and infrastructure

[155] RecruitIreland, http://www.recruitireland.com/careercentre/focuspharma.asp.
[156] van Egeraat, 2006, http://www.nuim.ie/nirsa/research/documents/WP%2028%20Chris%20van%20Egeraat.pdf

- The North-South Research Programmes that provide support for cross-border collaboration.

Since its inception in 1998, PRTLI has funded 47 research programmes. To date, over EUR 605 million has been allocated to the institutions of which EUR 295 million has gone to the bioscience sector with some 37% of the total amount having been spent by 2003[157]. The funding is distributed among several universities; University College Dublin was awarded EUR 35.9 million, University College Cork was awarded EUR 62.6 million, National University of Ireland was awarded EUR 28.8 million, and Trinity College Dublin was awarded EUR 46.2 million[158].

11.2.2.2 Science Foundation Ireland (SFI)

SFI is an organisation commissioned by the Irish government for the operation of the National Development Plan (NDP) 2007-2013 and the Strategy for Science, Technology and Innovation (SSTI) 2006-2013. The EUR 184 billion NDP[159] 2007-2013, is a seven year plan for building a wealthy Ireland, characterised by economic growth and balanced regional development. The NDP plan is the largest programme ever in Ireland and includes provision of EUR 54.6 billion for investment in economic infrastructure, EUR 25.8 billion for human capital such as schools and higher education, and EUR 20 billion for enterprises, science and innovation of which EUR 6.1 billion will go to science, technology, and innovation[160]. In total, EUR 8.2 billion has been allocated to scientific research under NDP and SSTI, of which EUR 1.4 billion is SFI's responsibility to invest. SFI offers grants to researchers wishing to relocate to Ireland and those already based in Ireland[161].

Some of the SFI programmes include Centres for Science, Engineering, and Technology (CSET) that support the development of new and existing Irish technology companies, attract companies to Ireland so they can affect the Irish economy, and expand educational and career opportunities. Strategic Research Cluster (SRC) is a programme linking scientists from academia

[157] Higher Education Authority, http://www.hea.ie/index.cfm/page/sub/id/543.
[158] Higher Education Authority, http://www.hea.ie/index.cfm/page/news/sub/755/section/NewsRelDetails/key/186.
[159] The National development plan proposes investment in Ireland's economic and social infrastructure, the enterprise, science and agriculture sectors, the education, training and skills base, and environmental services.
[160] *Ireland National Development Plan* 2007-2013, http://www.ndp.ie/documents/ndp2007-2013/NDP-2007-2013-English.pdf.
[161] Science Foundation Ireland, http://www.sfi.ie/content/content.asp?section_id=207&language_id=1

and industry to central research questions and influencing the development of Irish technology companies. [162]

11.2.2.3 Industrial Development Authority (IDA)

IDA is the Irish Government agency supporting inward investment and is actively seeking to attract investment from abroad in manufacturing and internationally trading service segments. IDA also encourages companies to expand their current investments in the country. During 2006, IDA invested in 54 R&D projects totalling almost EUR 470 million. The supported companies spent approximately EUR 15 billion in Ireland during 2006, of which EUR 2.8 billion was paid in corporation tax. In 2006, over 50% of employees in IDA-supported projects had wages and salaries levels of EUR 40,000 annually[163].

11.2.2.4 The Irish Venture Capital Association (IVCA)

Venture capital is a major driving force in the development of a knowledge-based economy in Ireland. With approximately 55 members, IVCA's role is to support industry research, develop professional standards etc. Outgoings on R&D by IVCA-supported high-technology companies represent 23% of total Irish spending on Business Expenditure on Research and Development (BERD). In 2005, IVCA gave EUR 89 million to technology firms for R&D, an increase of 34% since 2004[164]. Funds active in life science investment are ACT Venture Capital, that has completed over 70 investments mostly in technology-based companies, and the first science venture capital firm in Ireland, Seroba BioVentures, that invests in pharmaceutical biotechnology with a target size of up to EUR 25 million[165]. In 2002, Seroba BioVentures had already completed a first closing of EUR 15 million[166].

Enterprise Ireland, the government agency responsible for the development of Irish industry, assists companies with contacting Irish venture capital companies, such as IVCA, and does not finance companies. Under the National Development Plan 2001-2006, the government has committed EUR 95 million through Enterprise Ireland for partnering with the private sector in order to maintain the progress in the venture capital market[167].

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[162] Science Foundation Ireland, http://www.sfi.ie/uploads/documents/upload/SFI_Brochure.pdf.
[163] Industrial Development Agency, http://www.idaireland.com/home/index.aspx?id=8.
[164] The Irish Venture Capital Association, 2005, http://www.ivca.ie/eis_2005.pdf.
[165] Seroba BioVentures, http://www.seroba.ie/seroba/Main/Splash.htm.
[166] Seroba BioVentures, http://www.seroba.ie/seroba/Main/2002.htm.
[167] Enterprise Ireland, http://www.enterpriseireland.com/Grow/Finance/VentureCapitalists.htm.

11.2.3 Tax costs

The total corporation tax in Ireland is the lowest among all EU member countries, see figure 36 below. The corporation tax rate has been 12.5% since 1 January, 2003, and is charged on the profits, i.e. the business income, investment income and capital gains, of a company[168]. Until 1998, corporation tax in Ireland was 32%, between 1999 and 2003 the rate fell in stages as a result of an agreement between the Irish Government and the EU. Each year until 2002, the rate fell by 4%, and since then the rate has been 12.5%. The previous 10% *Manufacturing Rate of Corporation Tax* applicable to companies manufacturing goods in Ireland, or selling goods manufactured within Ireland at a 90% subsidy, is still available until 2010 when the final 12.5% rate will come into effect[169].

Figure 36: Corporation tax rates

Corporate tax rates	
Ireland*	12.50%
Singapore	20.00%
Netherlands	25.50%
United Kingdom	30.00%
China	33.00%
Belgium	33.99%
France	34.43%
Germany	38.60%
Japan	39.54%

*Tax on trading income

Source: Deloitte & Touche, 2007 and http://www.rikvin.com

11.2.3.1 R&D tax credit

In 2004, Ireland introduced a 20% R&D tax credit aimed at encouraging an increase in the amount of both foreign and domestic companies staring new and/or additional R&D operations in Ireland. The R&D tax credit is additional to the available corporation tax deduction of 12.5%, and applies to companies that own at least 50% of the company[170]. The company must also have expenditure arising from conducting R&D operations in the European Economic Area (EEA)[171]. The expenditure must be tax-deductible

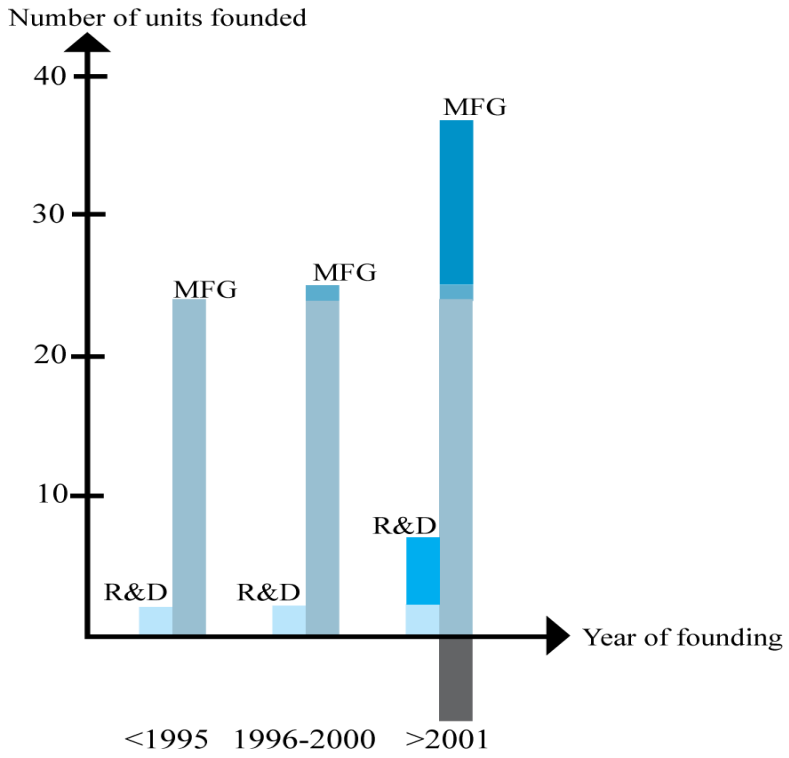
[168] Ireland Development Agency, 2007, http://www.idaireland.com/uploads/documents/IDA_Publications/Guide_to_Tax_in_Ireland_07_Final.pdf.
[169] LowTax Network, http://www.lowtax.net/lowtax/html/jirdctx.html.
[170] Ireland Development Agency, http://www.idaireland.com/home/index.aspx?id=681.
[171] EEA includes EU-27 plus Norway, Iceland and Liechtenstein.

only in Ireland, be in an investigative field of science or technology, and be available in a limited way to universities or institutes of higher education[172].

11.2.4 Business climate

Ireland has become an international pharmaceutical cluster because of the strong foreign investment by top international companies. According to our empirical data, the identification and mapping of big pharma companies, there is a total of eight R&D units of which three are in Cork and two in Dublin. There are 40 manufacturing units of which 13 are in Cork, and 13 in Dublin. Presently, 13 of the top 15 pharmaceutical companies in the world have substantial activities in Ireland in terms of manufacturing or R&D units. Some of the pharmaceutical companies with operations in Ireland are Pfizer, GlaxoSmithKline, Novartis, Johnson&Johnson, Merck, and Wyeth. Within the country, the pharmaceutical sector has its greatest concentration in the Cork area[173].

Figure 37: Units in Ireland



[172] PriceWaterhouseCoopers, 2004, http://www.software.ie/Sectors/ISA/ISADoclib3.nsf/wvICCS/0D712A2EDFE3C7AB80256EEB00546E79/$File/ICT+Ireland-PwC+summary+of+tax+credit+guidelines+July+04._g04k0_.pdf.
[173] Pharmacareers, 2007, http://www.pharmacareersireland.com/gpage5.html.

As presented above, Ireland is attracting mostly manufacturing operations. The manufacturing units have increased markedly during the time-period shown in the diagram, and R&D units have also increased. Three big pharma manufacturing operations have shut down in just a couple of years. The figure shows establishments of operations with a known founding year. Three manufacturing units are missing. Therefore, 37 manufacturing units are shown in the diagram but as mentioned before, in total there are 40 big pharma manufacturing operations in Ireland.

According to IDA (the government agency responsible for attracting foreign direct investment to the country) there are currently 83 pharmaceutical facilities with over 17,000 employees in Ireland, including big pharma. In 2003, the two counties of Cork and Dublin were estimated to account for 45% of all employment in pharmaceutical manufacturing. In the life science industry, Ireland has over 170 companies with 35,000 people are working in the pharmaceutical, biotechnology, and medical devices sectors[174]. The unemployment rate is 4.4%, amongst the lowest in the EU[175].

11.2.5 Infrastructure

A well-functioning infrastructure in a country affects competitiveness in several ways. It can reduce traffic congestion and delivery times, and increase consumer choice. Investment in the infrastructure has not kept up with economic growth in Ireland. Traffic in Ireland is heavy, broadband access is inadequate, and waste removal has room for improvement. According to OECD statistics, when comparing Ireland to other countries in regard to overall infrastructure, its ranking is one of the lowest. More specifically, Ireland ranked 22nd out of 25 in 2006. These rankings reflect deficits which need to be tackled. The National Development Plan 2007-2013 provides EUR 54.7 billion for investments in infrastructure. The total investment in transport infrastructure will be EUR 33 billion, with principal focus on building new national roads and public transport, and improving national airports[176]. Another issue in Ireland is industrial electricity prices which rose by 52% between 2002 and 2007. However, electricity prices did increase in other EU countries as well. In Ireland, to solve this problem the Commission for Energy Regulation (CER) has announced that there will be

[174] Ireland Development Agency, http://www.idaireland.com/home/index.aspx?id=64.
[175] Ireland Development Agency , 2007, http://www.idaireland.com/uploads/documents/IDA_Publications/Vital_Statistics_FINAL_May_2007_formatting_correct__4_.pdf.
[176] Ireland National Development Plan 2007-2013, http://www.ndp.ie/documents/ndp2007-2013/NDP-2007-2013-English.pdf.

an electricity price reduction of 4.4% for small business consumers and 8.4% for medium business consumers, from 1 November 2007. [177]

11.2.6 Metropolitan Cork area

Cork is the second largest city in Ireland after Dublin, with a population of 257,000 located in the south-west region in Cork County. Many foreign investors locate in or near Cork since it has a history of industrial development and business success. The Cork Area Strategic Plan (CASP) is a long-term plan until 2020, aimed at building a successful Cork by maintaining a well-qualified workforce, developing *clusters of excellence* that connect academic research and relevant companies with venture capitalists to encourage innovation and excellence, and much more. The Metropolitan Cork area has developed an industrial cluster, since a great many firms are located within the area and many are involved in similar enterprises. This strategy supports the bringing together of academia, venture capitalists, and other parties to foster greater innovation. Investors in the pharmaceutical and healthcare sector, and information and communication technology sector who make Cork their location are proof of the clustering strategy. This is evidenced by the fact that Ireland has the third largest concentration of pharmaceutical companies in the world due to 13 big pharma companies being located here[178].

11.2.6.1 Academia in Cork

University College Cork (UCC) has a commitment to excellence and its undergraduate and postgraduate programmes have contributed to the pharmaceutical and biotechnological successes of the region. Evidently, information technology is strong in Cork, particularly the computer science department at UCC, which is the largest growing section in the University with some 1,260 students. The Cork area is also home to the manufacturing services of most of the international pharmaceutical companies. Clearly, UCC is an important source of highly skilled students. In 1998, UCC initiated a BSc degree programme in pharmaceutical chemistry. The University ensures that students are integrated into the pharmaceutical sector after their education. During 2003, the University started a new pharmacy degree programme focusing on scientific and clinical regulations[179].

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[177] Forfas, 2007, http://www.forfas.ie/publications/forfas071112/overview_infrastructure_issues_2007.pdf.
[178] Cork City Council, 2005, http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf.
[179] Ibid.

The links between UCC and the industry have made Ireland a good research base. During 2002-2003, the gross income of the University from councils for scientific evaluations, (known as peer-reviewed sources) passed EUR 44 million. These research activities have been supported by the University through EUR 100 million in funds investment from the National Development Plan. The University's goal is to maintain the position in this area. During 2004-2005, research income was about EUR 46 million. Since 2000, UCC has accepted EUR 70 million for over 30 research programmes financed by Science Foundation Ireland (SFI). These include the Bioscience Institute that focuses on cancer and cell signalling plus analytical neuroscience, the Biological Chemistry Research Institute that investigates the design and development of new pharmaceutical agents and the National Microelectronics Research Centre, which focuses on research into optoelectronics, and nano-scale science and technology[180]. Another major collaborative research project into gastrointestinal diseases, established at UCC by GlaxoSmithKline (GSK), is jointly supported by IDA Ireland and SFI and involves up to EUR 13.7 million. Researchers from GlaxoSmithKline's Gastrointestinal Centre are working closely with researchers at UCC, to identify new drug targets for the treatment of bowel disease. Such research projects, involving a high-level collaboration between a major pharmaceutical company and one of the top universities in Ireland, represent the government's strategy to promote industrial-academic collaborations[181]. In 2005, UCC received a total of EUR 62 million from various sources, such as the European Union, government departments, SFI, industry etc. The industry contributed approximately EUR 6 million[182].

Cork Institute of Technology (CIT) offers courses in Science, Computing, Business, and Engineering etc. CIT has a good relationship with the industry; exchange programmes, and industrial job positions are examples of such collaborations. The Institute includes a range of specialist technology centres offering independent advice, expertise and assistance to diverse segments of industry, business, and government. Research and development is an important part of the relations between the Institute and the industry. Like many others, the institute offers postgraduate research programmes. Expertise and advice can be also be offered since the Institute

[180] Ibid.
[181] Ireland Development Agency, http://www.idaireland.com/home/news.aspx?id=9&content_id=608.
[182] University College Cork, *Research at UCC,* 2006, http://www.ucc.ie/en/ResearchandIndustry/OfficeoftheVPforResearch/Research/DocumentFile,16285,en.pdf.

includes specialist technology centres that receive funding from the EU and industry sectors[183].

11.2.7 Innovation milieus

Metropolitan Cork anticipates its future as a centre of innovation and inspiration for new ideas. The process has already begun, throughout the *Knowledge Zone* and the *National Microelectronics Research Centre (NMRC).*

Knowing that proximity is important for knowledge-based companies, the *Knowledge Zone* is located in the south west of Cork. The Zone offers companies an opportunity to locate close to city seats of learning so that they can create strong relationships and share knowledge with researchers and other highly skilled people. This idea is about eliminating barriers so that ideas and innovation will flow and create economic development in Ireland[184].

The National Microelectronics Research Centre (NMRC) is an information and communications technology (ICT) research institute within UCC involved in a number of research projects at national and international level. It is the largest multidisciplinary research centre in Ireland and is known as a centre of excellence in the ICT field. The focus areas of research are in nanotechnology, microtechnologies, and photonics. The Irish ICT segment is the largest single manufacturing sector in Ireland. With the industry and the government agencies, the Irish economy and research will develop to make NMRC more powerful than it is today[185].

11.2.8 University technology transfer

Technology Transfer Initiative (TTI) is a project co-funded by the participating universities and Enterprise Ireland under the National Development Plan 2000-2006. TTI helps companies access the expertise and resources of the universities, such as University College Cork, University of Limerick, and National University of Ireland. The TTI's goal is to encourage and support Irish companies to become more innovative, more competitive, and to develop strong relationships with companies within four sectors: pharmaceutical/biotechnology, information and

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[183] *Strategic Cork*, 2005, http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf.
[184] *Strategic Cork*, 2005, http://www.corkcity.ie/strategiccorkguide/competitive_edge/innovation_and_entrepreneurship.shtml.
[185] *Strategic Cork*, 2005, http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf.

communication technology (ICT), engineering, and food. TTI can also enhance the information and assistance to companies engaging in R&D[186].

Started in 2003, *NovaUCD* is an EUR 11 million Innovation and Technology Transfer Centre in University College Dublin. NovaUCD has a goal to become one of the world's leading commercialisers of research activity. Today, NovaUCD is responsible for commercialising UCD research and for the progress of co-operation with industry and business. NovaUCD, with over 40 incubation units, offers start-up companies a full business support programme including advice, consultancy, and training. In addition,companies can contact NovaUCD for contact with partners seeking collaborative research[187].

11.3 Singapore

11.3.1 History

During the 1960s, Singapore was a small country with no natural resources and its population was approximately 1.6 million. Singapore was a third world country; its gross national product (GNP) was USD 320 per capita, the infrastructure was inadequate, and there was no direct foreign investment in the country. It needed to create jobs, but to do that there had to be industrial development. Thus, the Jurong industrial area along the west coast was born, which began with manufacturing works for textiles, wood products, and toys. Singapore Economic Development Board (EDB) was founded in 1961and invested USD 100 million in infrastructure to convince foreign investors that the country was a great place to do business.

In the 1970s, unemployment was no longer a problem and the EDB started exporting oriented industries and marketing Singapore as a start-up location with a ready workforce. Industry in Singapore widened; there were no longer just wood products or toy production, and new investments in electronics enhanced the export and investments in Singapore. In 1981, the minister of Trade and Industry, Goh Chok Tong said, *"The plan is to develop Singapore into a modern industrial economy based on science, technology, skills and knowledge."*[188] To achieve what the minister had promised, the EDB renewed its emphasis on manpower development. This took place through the science park set up next to the National University of

[186] University College Cork, http://www.ucc.ie/en/ResearchandIndustry/OfficeoftheVPforResearch/IndustrialLiaisonandTechnology/Transfer/TechnologyTransferInitiative/ .
[187] University College Dublin NovaUCD, http://www.ucd.ie/nova/.
[188] Singapore Economic Development Board, http://www.edb.gov.sg/edb/sg/en_uk/index/about_us/our_history.html.

Singapore to stimulate research and development activities. Institutes of technology were also jointly established with the governments of Japan and France. During the 1980s and 1990s, 7,000 multinational companies were established in Singapore and the cluster development begun[189].

11.3.2 Life science policy in Singapore

In Singapore, the aim is to become a centre for knowledge, talent, and business. To achieve this, government grants help companies to start up, sustain, and grow their businesses. For industry development, the government offers assistance such as loans, grants and tax incentives.

11.3.2.1 Grants

The life science cluster receives grants from two main sources; the Agency for Science, Technology and Research (A*STAR) and the Economic Development Board (EDB).

11.3.2.2 A*STAR

A*STAR's mission is to promote world-class scientific research. It includes the Biomedical Research Council (BMRC), the Science and Engineering Research Council (SERC) and many more. The BMRC and SERC support and manage the public sector biomedical research and development in Singapore. The BMRC strengthens fields such as pharmaceuticals, medical devices, biotechnology, and healthcare services within the biomedical field whilst the SERC strengthen electronics, chemical, and engineering clusters. Since its inception in 2000 and up until 2005, BMRC has awarded 264 extramural grants totalling some USD 195 million in research funding[190]. Averaging USD 500,000 per project, the SERC grants are awarded to research projects covering such areas as electronics, chemistry, physics etc. The funding period is typically three years; in 2001 a total of USD 8.04 million was granted to 16 projects[191].

11.3.2.3 EDB

EDB is the lead government agency providing investments to stimulate the domestic economy. EDB focuses on manufacturing and related services as well as exportable services sectors. In 2005, EDB distributed USD 100

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[189] Ibid.
[190] Singapore Economic Development Board, 2005, http://www.sedb.com/edb/sg/en_uk/index/news_room/news/2006/biomedical_sciences.html.
[191] Agency for Science, Technology and Research, 2006, http://www.astar.edu.sg/astar/about/action/pressrelease_details.do;jsessionid=A44ADA6104FA7E8BB3669F9A51064D1A?id=0e0d5538216u.

million to attract investment to the manufacturing sector, these investments contributed to 18,000 jobs, of which approximately 70% were skilled[192].

Part of EDB is the Business Angels Scheme (BAS) that provides capital for start-up companies or innovative firms that are less than five years old and developing new products. The BAS will invest up to USD 1 million in a company. This scheme is similar to the EDBs Start-up Enterprise Development Scheme (SEEDS) in encouraging business investment in innovative start-up firms. SEEDS finance companies up to USD 300,000, but the investor must put in at least USD 75,000 and the start-up company has to be incorporated for less than three years in Singapore. For small companies with less than 10 employees, the Micro Loan Programme provides loans of up to USD 50,000 at fixed or variable rates[193].

For the R&D sector, the government invested USD 660 million in 2005 to strengthen the R&D potential of Singapore. Of the USD 660 million, USD 543 million went to the public sector research in areas such as science, engineering, and biomedical sciences. For the private sector, USD 117 million went through the Research Incentive Scheme for Companies (RISC) to promote private sector R&D ventures in Singapore. RISC offers project-based funding to firms to support the R&D capability[194].

11.3.3 Venture capital

The private sector investment in venture capital is not yet well-developed in Singapore. Over 150 venture capital companies are currently located in Singapore and they jointly contribute USD 12 billion of funds with a large amount directed to the biomedical industry. More specifically, 25% of these firms are domestic, 40% are from North America and Europe, and the remaining 35% are from Asia[195]. Although companies can go directly to venture capitalists for funding, many choose to use matchmaking channels to find a venture capitalist that can meet the specific demands of the company. One of these is Singapore Venture Capital Association (SVCA) that started in 1992 under the support of EDB, with the aim to promote, develop, and foster industry growth. To do this, SVCA facilitates link

[192] Singapore Government, http://www.mof.gov.sg/budget_2005/expenditure_overview/mti.html.
[193] Singapore Government, http://www.spring.gov.sg/Content/WebPageLeft.aspx?id=b859b2c6-093a-4e75-9f0e-1c5bf2792a9c.
[194] Singapore Government, http://www.mof.gov.sg/budget_2005/expenditure_overview/mti.html.
[195] Singapore Economic Development Board, 2002, http://www.sedb.com/edb/sg/en_uk/index/news_room/news/2002/speech_by_mr_teo_ming0.html.

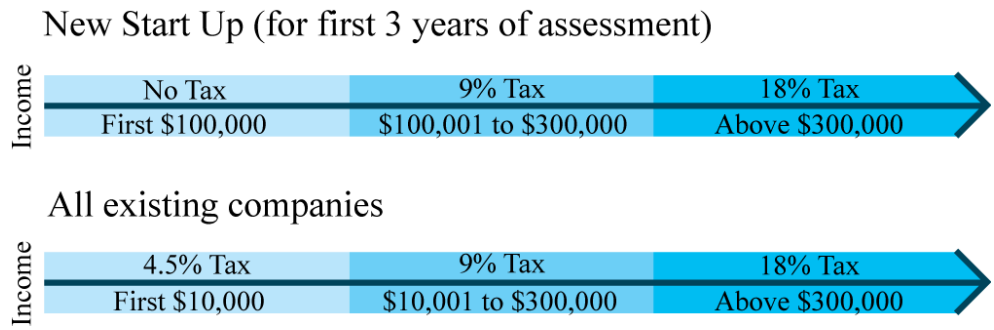
between firms seeking finance and venture capital companies, as well as interaction among professionals in the venture capital and private equity industry[196].

11.3.4 Tax cost

Corporation tax is being cut in many countries, especially in Europe. In order to help keep Singapore attractive as a business location, corporation tax rate will be reduced from 20% to 18% in 2008[197]. With the current 20% corporation tax being higher than some competing countries, such as Ireland with its 12.5%, this corporation tax cut will enhance the competitiveness of Singapore as a business location.

Today, there is a zero tax rate for new start-up companies for the first three years of incorporation. Thereafter there is partial tax exemption with a rate of 5% for the first USD 10,000 of income and 10% for the next USD 90,000. As from 2008, there will be a zero tax rate for the first three years or for the first USD 100,000, and thereafter a 9% tax rate on annual profits for the next USD 290,000. For existing companies with a USD 10,000 income, there will be a 4.5% tax rate as from year 2008, and thereafter a 9% tax rate for income of up to USD 300,000[198], see figure 37.

Figure 38: Singapore corporate tax



Source: http://www.mof.gov.sg/budget_2006/budget_speech/subsection6.2.html

11.3.5 Infrastructure

Singapore is well connected to the rest of the world; the Singapore Changi Airport has a vision of becoming one of the best airports in the world, it has

[196] The Singapore Venture Capital and Private Equity Association, http://www.svca.org.sg/about1.htm.
[197] International Enterprise Singapore, http://www.iesingapore.gov.sg/wps/portal/!ut/p/kcxml/04_Sj9SPykssy0xPLMnMz0vM0Y_QjzKLN4g38nAHSYGYjvqRMJEgfW99X4_83FT9AP2C3IhyR0dFRQBOc5AF/delta/base64xml/L3dJdyEvd0ZNQUFzQUMvNElVRS82XzlfMUZC.
[198] Singapore Government, 2006, http://www.mof.gov.sg/budget_2006/budget_speech/subsection6.2.html.

repetitively been named the best airport in the world. It serves over 60 airlines to over 145 cities and provides speedy and unproblematic clearance. For arriving passengers, it takes totally 30 minutes to clear immigration, claim baggage, and pass customs.

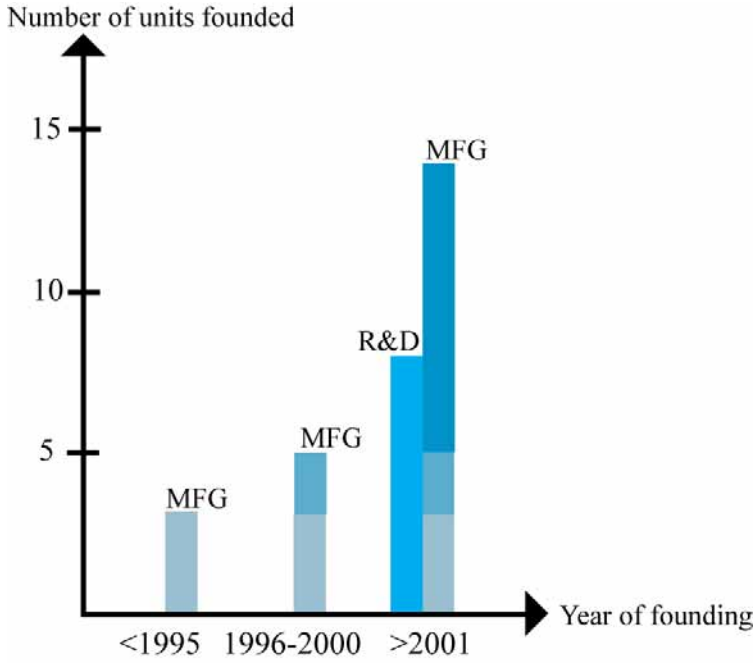
11.3.6 Business climate

Singapore has set its sights on becoming the life science centrality of the Asia Pacific region, due to its excellent international pharmaceutical companies, hospitals, and universities. It also has strong links between universities, hospitals, and industry. According to our empirical data, there are eight R&D units, and 14 manufacturing units from big pharma in Singapore. Singapore is home to seven of the top ten pharmaceutical companies in the world, such as Pfizer, GlaxoSmithKline, Sanofi-Aventis, Novartis, Merck and many more. The companies' manufacturing operations focus on microbial fermentation, animal cell technology, downstream purification, and analytics[199], while R&D-intensive companies in Singapore mainly focus on stem cell research to find treatments for diseases such as diabetes, CNS neurodegenerative disorders, and cancer[200].

The figure below shows how fast big pharma companies are establishing themselves in Singapore. From 2001 and onwards the number of manufacturing units has almost trebled and R&D units have increased significantly from zero to eight R&D units in just six years. The founding years of all identified units in Singapore have been included.

[199] Singapore Economic Development Board, 2004, http://www.edb.gov.sg/edb/sg/en_uk/index/news_room/news/2004/pfizer_opens_new_manufacturing.html?showMode=printable .
[200] Agency for Science, Technology and Research, 2004, http://www.a-star.edu.sg/astar/attach/textlet/2937a36dcfiC/Scholars_Voice_BMS_EU_IP_Trip_Report_Nov_04.pdf.

Figure 39: Units in Singapore



The economy of Singapore grew by 7.9% in 2006 and total employment expanded by 7.6%, creating 176, 000 jobs. Between January and September 2007, 171,500 new jobs were created in Singapore, almost the same number of job creations for the whole of 2006. Meanwhile, the unemployment rate fell from 3.1% in 2005 to 1.7% in 2007, its lowest since 1996[201]. Singapore has approximately 2.0 million workers, of which 10,571 people work within the biomedical sector. Of the total workforce of 10,571in the biomedical field, 4,020 work within the pharmaceutical sector and the remaining 6,551 work in the medical technology field[202].

11.3.7 Academia

National University of Singapore (NUS), located in southwest Singapore at Kent Ridge was established in 1905 and has over 32,000 students from 88 countries, which makes NUS a global university. NUS seeks to provide high quality education which allows students to realise their potential. In 1998, the NUS, the Nanyang Technological University and Massachusetts Institute of Technology (MIT) formed an alliance to promote engineering and life science education and research collaboration among these

[201] FinMarket, 2007, http://www.wrestling.kiev.ua/en/news_forex/detail/170742/2/0/1193781600/.
[202] Agency for Science, Technology and Research, 2006, http://www.biomed-singapore.com/etc/ medialib/bms_downloads/newsroom.Par.0004.File.tmp/Factsheet%20-%20BMS.pdf.

universities[203]. Nanyang Technological University is a research-intensive university in Singapore with a focus on science and engineering.[204] There are about 1,000 research collaborations each year, with strong relationships between academia, industry, and government. One of these is a collaboration between NUS, MIT, and Ohio State University to study the parasite *Plasmodium falciparum* that causes malaria. Another collaborative research project is the Singapore Chinese Health Study between NUS and the University of Southern California investigating dietary and other environmental determinants of chronic diseases. Since 1993, the study has been supported by the National Cancer Institute in the US and has so far been granted some USD 8 million[205].

11.3.8 Innovation milieus

11.3.8.1 Biopolis

In an effort to attract foreign companies to set up business in Singapore, Biopolis was established for ease of relocation and to provide common facilities for start-up companies focusing on R&D. Biopolis is a nine-building complex with 185,000 m^2 of space that allows for collaboration among research institutes, private research organisations, and biomedical universities, such as the National University of Singapore and National University Hospital. The Biopolis complex is home to over 2,000 researchers and technicians, and by the end of 2009, an additional 74,000 m^2 of space will be completed for building up a world-class research area. Five of the nine buildings accommodate A*STAR's research institutes such as the Institute of Molecular and Cell Biology, the Genome Institute of Singapore and so on. In two other buildings, about 20 companies have set up R&D facilities, including GlaxoSmithKline and Novartis. The Biopolis area is the largest infrastructural project initiated by the Singapore government. Biopolis allows start-up companies to reduce their R&D costs by taking advantage of shared facilities and shared scientific equipment such as X-ray crystallography and MRI equipment. Companies have also access to shared infrastructure such as conference and meeting facilities[206].

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[203] National University of Singapore, http://www.chee.nus.edu.sg/highlights/SMA-2-CPE-Briefing30Nov.pdf.
[204] Nanyang Technological University, http://www.ntu.edu.sg/publicportal/about+ntu/about+us/intro.htm.
[205] National University of Singapore, 2003, http://www.nus.edu.sg/ore/publications/quest/03_Research%20Collaboration%2019-26.pdf.
[206] International Enterprise Singapore, http://www.biomed-singapore.com/etc/medialib/bms_downloads/newsroom.Par.0010.File.tmp/BIOTECH%200708.pdf.

11.3.8.2 Tuas Biomedical Park (TBP)

Tuas Biomedical Park (TBP) is a world-class manufacturing hub for the biomedical sector, dedicated to pharmaceuticals, biopharmaceuticals, biologics, vaccine, and medical devices companies. It is designed to support manufacturers with an environment that provides power, water, telecommunications, and gas requirements. Today, TBP occupies an area of over 360 hectares and some of the world's leading pharmaceutical companies are located there, including GlaxoSmithKline, Merck, Pfizer and many others. By locating there, these companies can benefit from shared facilities, strong intellectual property protection, and strong government support[207].

11.3.8.3 NUS Enterprise (ETP)

ETP was established in 2001 at the NUS to provide an entrepreneurial and innovative aspect to education and research. The ETP strategy is to create an entrepreneurial culture for start-up enterprises, by teaching, training, and internships for talented people. This is done by means of the support of NUS Overseas Colleges (NOC), the Industry Liaison Office (ILO), and NUS Entrepreneurship Centre (NEC). NOC offers an educational programme that provides students opportunities to engage themselves in activities of start-ups. The internship experience will lead towards the development of an entrepreneurial NUS area with a global mind-set. ILO serves as a link between companies, research organisations, and government agencies so they can access technologies and the knowledge in NUS. ILO also protects NUS' intellectual property, and contributes support to develop discoveries and innovations into products by NUS researchers. NEC offers educational programmes within innovative entrepreneurship that provide practical involvement and learning in the entrepreneurial progression[208].

11.3.9 Research centres

Set in the Biopolis, the *Genome Institute of Singapore (GIS)* has been given a USD 167 million research grant, mainly from A*STAR, to integrate new technologies which identify novel genes and molecular targets in diseases common to the Asia-Pacific region. The focus is mostly on cancer and infectious diseases. The GIS is planned to help the growth of the life science industry in Singapore. To do this and make the institute competitive, GIS hired some 250 professional scientists from all around the world between 2005 and 2007. One important goal for Singapore is to establish a genomic

[207] Singapore Government, http://www.jtc.gov.sg/portfolio/tuasbiomedicalpark/fast%20facts/pages/index.aspx.
[208] National University of Singapore, http://www.nus.edu.sg/enterprise/aboutus/index.html.

knowledge base to anchor research institutes and pharmaceutical companies to make Singapore more attractive to foreign investors[209].

The Institute of Molecular and Cell Biology (IMCB) was established in 1987 at the National University of Singapore, it has a mission to develop research culture for biomedical science thus supporting the development of biotechnology in Singapore. The IMCB is primarily funded by the BMRC of A*STAR, employing over 400 scientists that mainly focus on cell cycling, cell signalling and cell death. In 2004, IMCB moved to the Biopolis to join the biomedical research institutes. Research collaborations have been established with industry, research institutions, and universities globally, including Harvard Medical School (USA), University of Gothenburg (Sweden), University of London (England) and many more. IMCB also collaborates with many pharmaceutical companies such as Pfizer, Genzyme, and Merck[210].

11.3.10 University technology transfer

11.3.10.1 NUS Industry Liaison Office (ILO)

In support of the university drive to become a global entrepreneurial university, ILO, a part of the NUS Enterprise set up in 1992, is active in creating relationships with top universities and technological commercialisation groups around the world. ILO helps to translate new discoveries by NUS researcher into new products and services via certificating these technologies to existing or new companies. Meanwhile, ILO facilitates university collaboration with the industry through industry-sponsored research and projects, and protects and manages the intellectual property of the university. ILO's vision is to be a leading university intellectual property management and technology transfer office in the Asia-Pacific region. NUS have regular discussions with industry and agencies to get a better understanding of the R&D needs for the industry. The collaboration between industry and NUS helps keep industry updated of latest developments while maintaining NUS relation to its partners in industry[211].

[209] Genome Institute Of Singapore, 2007, http://www.gis.a-star.edu.sg/internet/site/article_data/ GIS_Brochure.pdf.
[210] The Institute of Molecular and Cell Biology, http://www.imcb.a-star.edu.sg/about_imcb/annual_report/report2005-2006.pdf.
[211] National University of Singapore, http://www.nus.edu.sg/enterprise/enterprisecluster/ilo.html.

11.4 Switzerland

11.4.1 History

The life science industry's origins can be traced back to the 19th Century when chemical manufacturers like Hoffman-La Roche (today Roche), Ciba, Sandoz, and Geigy started pharmaceutical operations in Switzerland[212]. Many of these companies moved into basic research and production and the industry expanded quickly in the 60s, when Switzerland also decided to invest a lot of money in biological research[213]. In the 1970s Ciba and Geigy merged. After the two companies established a factory in New Jersey, they discovered the benefits of combining pharmaceutical research, and formed one of the world's leading pharmaceutical companies, Ciba-Geigy. In 1996, Ciba and Sandoz merged and formed Novartis, one of the largest enterprise mergers[214]. Another world-leading pharmaceutical company is Serono, which has now been acquired by the German company Merck KGaA. Switzerland, a small country with a relatively high number of big pharma companies, is considered an attractive location for the pharmaceutical industry[215].

11.4.2 Life science policy in Switzerland

The Confederation, the Swiss union of cantons, has a responsibility for science and technology which is mainly discharged through the Federal Department of Home Affairs (FDHA), a government unit that is a part of the Swiss Federal Council. The FDHA promotes the financial aspects of education and the promotion of finance activity in the science and technology sector, through the agency of the State Secretariat for Education and Research (SER). In 2007, SER spent CHF 1.7 billion in subsidies to various objects[216], see figure 39.

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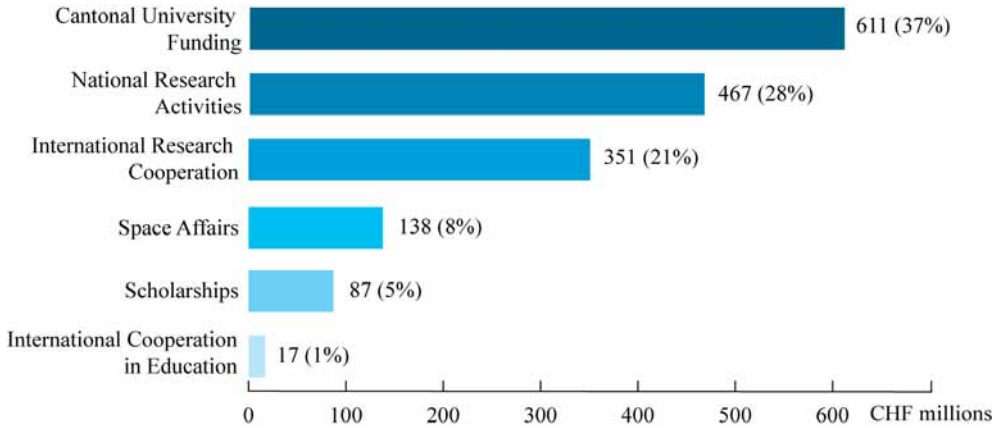
[212] *History Of Switzerland*, http://history-switzerland.geschichte-schweiz.ch/industrialization-switzerland.html.
[213] Ernst&Young, Swiss Exchange, Seco, KTI & Swiss Biotech, 2005, http://www.greaterzuricharea.ch/content/04/downloads/swiss_biotech_report_2005.pdf.
[214] FundingUniverse, https://www.fundinguniverse.com/company-histories/CibaGeigy-Ltd-Company-History.html.
[215] Houlton, 2002, http://www.users.globalnet.co.uk/~sarahx/articles/cwswiss.htm.
[216] State Secretariat for Education and Research SER, http://www.sbf.admin.ch/htm/sbf/zahlen_en.html.

Figure 40: SER Subsidies in 2007 by area of focus



Source: http://www.sbf.admin.ch/htm/sbf/zahlen_en.html

11.4.2.1 The Swiss National Science Foundation (SNSF)

The Swiss National Science Foundation (SNSF) was established in 1952, mandated by the federal government as an instrument of research funding. SNSF is mainly financed by the Confederation, through SER. SNSF annually supports approximately 7,000 scientists, performing basic research in various disciplines, such as philosophy, biology and medicine. In 2006, SNSF had a total expenditure of CHF 491 million in research financing. Research in the humanities and social sciences received 25% of the grants, 35% went to projects on mathematics, natural and engineering sciences and 40% went to research into biology and medicine. The funding options in any discipline include project funding, individual and career development funding, and grants toward publication costs etc[217].

11.4.2.2 The Commission for Technology and Innovation (CTI)

The CTI is an innovation promotion agency of the Swiss Confederation established in 1951. It is mandated by the FDHA and funded by the Federal Office for Professional Education and Technology (FOPET). Its mission is to support start-up companies, generate innovation, and to transfer knowledge and technology between universities and businesses. CTI provides support to young entrepreneurs through its training programme *venturelab* and promotes the foundation of businesses. Every year, CTI finances several hundred R&D projects that companies implement in collaboration with universities. The funding is available for all disciplines. Between 2001 and 2005, some 1,500 R&D projects were supported, and between 2004 and 2007 the CTI budget amounted to CHF 400 million. Since 1996, over 140 start-up companies have been funded by CTI, and

[217] Swiss National Science Foundation, http://www.snf.ch/e/aboutus/seiten/default.aspx.

today 85% of these are still in business, having created over 4,000 new jobs in Switzerland[218].

11.4.3 Venture capital

Switzerland has over 40 venture capital firms and private equity funds. Private equity refers to equity investments in non-quoted, privately held companies. In 2006, a strong development of the private equity industry could be seen, 79.6% of the funds raised originated from abroad which may indicate that Switzerland is a strong life science cluster in that it attracts foreign venture capitalists to Switzerland and develops a domestic private industry. Domestic private equity investments amounted to EUR 583.3 million, in 2006. Between 2005 and 2006, the funds raised amounted to EUR 1.6 billion, which corresponded to a 9.4% increase. The major source of funds is the government agencies that accounted for 24.5% of the grants, followed by insurance companies at 22%, and pension funds at 18.7%[219].

11.4.4 Tax cost

Swiss taxes are among the lowest in Europe, both for companies and individuals. The effective corporation tax rate comprises federal and cantonal taxes. Switzerland has 26 provinces or cantons and the federal corporate income tax rate is 8.5% throughout Switzerland as well as each of the 26 cantons having its own separate tax rate. Today, Canton of Zug is the most tax-favourable canton, with a maximum of tax on corporate profits of 17.8%, as compared with approximately 25% in the rest of the country[220]. All cantons offer tax relief to attract foreign companies and encourage start-up companies. The tax relief is a form of a participation exemption that applies to Swiss companies with substantial participants. For example, for mixed holding companies the tax relief is calculated according to the percentage of the total net income arising from participations. To qualify for relief, the participation must comprise at least 20% of the company or exceed CHF 2 million in fair market value. For pure holding companies, there is a holding privilege, almost a complete exemption from tax at cantonal level, but it does not require active business, just holding activity, and 2/3 of the total assets (or income) must consist of participations. When these requirements are met, pure holding companies pay just 8.5% federal tax on their income. According to domiciliary companies (companies which only have administrative activities in Switzerland, such as their

[218] Federal Department of Economic Affairs, retrieved 7 December 2007, http://www.bbt.admin.ch/kti/org/00278/index.html?lang=en.
[219] European Venture Capital and Private Equity, 2007, http://www.seca.ch/sec/files/statistiks/Switzerland_2007.pdf
[220] Bachmann, 2007, http://www.time.com/time/magazine/article/0,9171,1000091,00.html

headquarters, and all or the major part of their business activities abroad) the federal tax cannot be reduced. For new companies, tax relief is also granted to attract investments[221].

11.4.5 Infrastructure

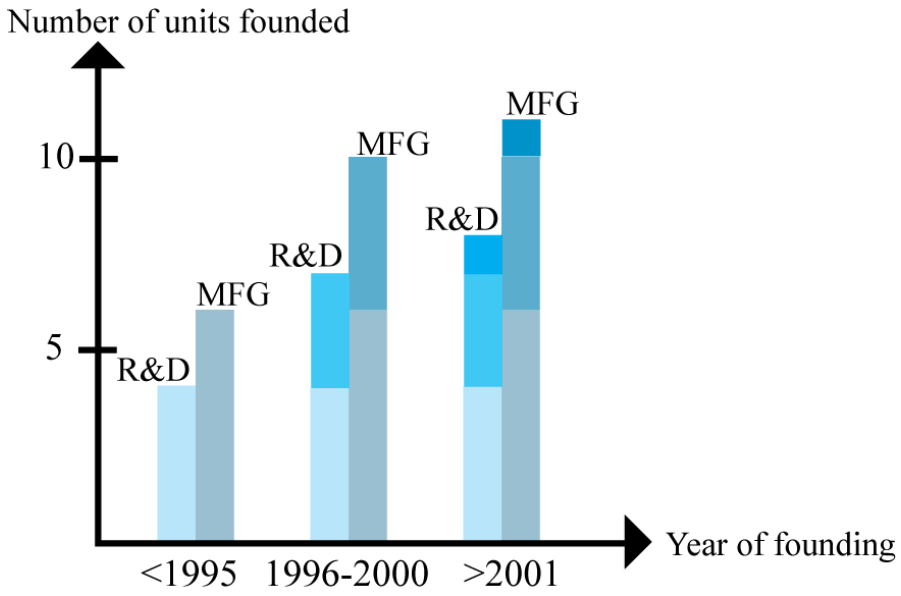
Since Switzerland is located at the heart of Europe, it is a prime communications hub for life science in Europe, with an extremely good infrastructure. There are three major airports that offer direct international flights. One of these is Zurich airport, which currently offers 120 destinations in over 70 countries. The two other international airports are Basel and Geneva and provide a large number of flights to many important business centres, and some direct flights to overseas destinations. For road transportation, the Swiss network of freeways is one of the world's most compact, with four-lane highways interconnecting all parts of the country[222]. There is high-quality public transport. The *Swiss Travel System* is a network of trains, buses, and ships. Most of the cities are connected by InterCity trains, but they run once per hour. For local buses, the network offers daily service from 5:30 a.m. until midnight and every six minutes during rush hour[223].

11.4.6 Business climate

Geographically, the majority of the pharmaceutical companies are located in or around: Basel, Geneva/Lausanne, Lugano, and Zurich. From our compiled data, three big pharma companies are headquartered in Switzerland. There are 20 manufacturing units and 11 R&D units. Switzerland houses 13 big pharma companies, such as Novartis, Johnson&Johnson, Abbott Labs, and Roche.

[221] Taxation, http://www.taxation.ch/index.cfm/fuseaction/show/temp/default/path/1-535.htm
[222] Federal Administration, http://www.locationswitzerland.admin.ch/themen/00469/index.html?lang=en .
[223] Travel guide to Switzerland, http://www.myswissalps.com/switzerland/switzerland-transportation.asp?lang=EN.

Figure 41: Units in Switzerland



The accumulation diagram above gives an overview of big pharma establishments in Switzerland. Since there are no founding years for nine of the manufacturing units and three of the R&D units, the diagram is not complete. The compiled data of big pharma companies does not show any plant closures in Switzerland.

In 2006, the four main bio-pharmaceutical clusters in Switzerland included 251 biopharmaceutical companies, specifically:

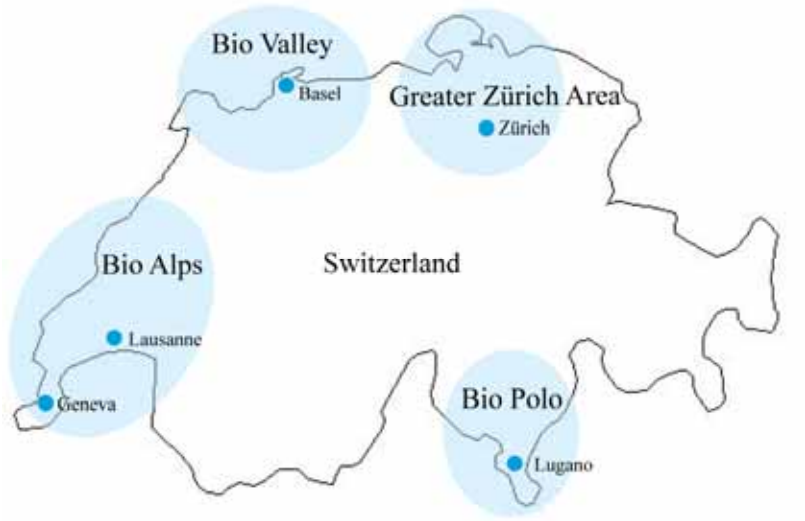
1 Bio Valley in Basel with 64 companies.
2 Greater Zurich area with 96 companies.
3 Bio Alps by Lake Geneva with 70 companies.
4 Bio Polo Ticino in the Lugano area with 21 companies.

A total of 286 biopharmaceutical companies operate in Switzerland. The country boasts the highest per capita company density. Biovalley is one of the most important pharmaceutical clusters in the world and home to multinationals Novartis, Roche, and Merck Serono. The most prominent areas of bioscience in Biovalley are oncology, immunology and neuroscience[224]. Bio Polo Ticino is a biotech platform for technology transfers and business development; Bio Alps has science parks, and the Greater Zurich Area has the highest per capita density of biotech companies

[224] Capgemini, 2004, http://www.biovalley.ch/downloads/downloads_files/BioValley_Cluster_Analysis_Final_Summary_18.10.04.pdf.

in the world[225]. In 2004, the pharmaceutical industry employed over 31,000 people in Switzerland. This corresponds to 0.7% of total employment[226].

Figure 42: Map of Switzerland showing the clusters



Source: http://www.biopolo.ch/Products/Swiss%20LifeScience%20Survey%202006.ppt#2

11.4.7 Academia

11.4.7.1 University of Basel

The University of Basel is the oldest university in Switzerland, established in 1459. The Biozentrum department opened in 1971 and is a basic research institute focusing on the research areas of biochemistry, microbiology, structural biology, and cell biology. The purpose of the Biozentrum is to unify biological and natural sciences in the same building, making collaboration with other research areas possible. The University of Basel, together with Basel Institute of immunology[227] (Roche), and the Friedriche Miescher Institute for Biomedical Research (part of the Novartis Research Foundation) made Basel a focal point for research collaboration in the life sciences[228]. The biological research studies are divided into three steps: firstly, basic studies taking four years, with the last year consisting of practical work in research groups; secondly, PhD studies requiring 3-4 years

[225] Swiss Life Sciences Database, 2006, http://www.biopolo.ch/Products/Swiss%20LifeScience%20Survey%202006.ppt#2.
[226] Plaut Economics, , 2005, http://www.interpharma.ch/fr/pdf/Bericht_Interpharma_def_f.pdf.
[227] The Basel Institute of Immunology was founded in 1969 by F. Hoffman-La Roche, which is one of the world's foremost basic research establishments in the field of immunology.
[228] *Life Science Brochure,* http://www.baselarea.ch/uploads/media/Life_Science_broschuere_englisch_02.pdf .

of research; and, thirdly, there are postdoctoral studies with international exchange programmes.[229]

11.4.7.2 University of Zurich

Founded in 1833, the University of Zurich is the largest university in Switzerland; it is devoted to scientific research and teaching, which are highly linked. The University has approximately 24,000 students, including both undergraduate and postgraduate, and 14% of these are students from other countries. From its beginning, a total of 12 Nobel Laureates have held professorships at the University of Zurich. The University offers service to the public in connection with research and teaching. The hospitals and medical centres are affiliated with the University and there is a combination of medical care with scientific activities in research and teaching. As with many other universities, collaboration with other universities is common. For example, the University works in partnership with the Federal Institute of Technology (ETH) Zurich in the project Life Science Zurich[230]. Life sciences at the University of Zurich and ETH consist of research and teaching in disciplines such as natural sciences, biology, chemistry, and physics. The goal is to maintain a leading position in the research of the disciplines[231].

11.4.8 Innovation milieus

11.4.8.1 TechnoParc Zurich

TechnoParc Zurich was established in 1993, and its mission was to support start-up companies by offering top technological performance with established companies and research groups in many disciplines. This collaboration conduces experience and inspiration interchange. The Park is the biggest innovation centre in Switzerland, with 44,300 m^2 space, employing about 1,400 people in 190 companies and organisations. The TechnoPark helps enterprises implement new technologies, solve business problems and access key partners. Start-up companies need access to venture capitalists, business angels (private investors), and seed money providers and bankers but with the assistance of TechnoPark, it is possible to interact with them. This innovation centre is a private company with a foundation that promotes technology transfer through a network available to science and industry. Apart from the network, it supports all technology-oriented start-up companies[232].

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[229] The Biozentrum of the University of Basel, http://www.biozentrum.unibas.ch/ataglance.html.
[230] The University of Zurich, http://www.uzh.ch/about/portrait/info_uzh_en_2005.pdf.
[231] Life Sciences in Zurich, http://www.lifescience-zurich.ch/inzuerich/index-en.asp.
[232] Technopark Zurich, retrieved 18 December 2007, http://www.technopark.ch/estart.cfm.

11.4.8.2 Park Allschwil

The innovation centre of north-western Switzerland in the Basel area, namely Park Allschwil, was established in 1997. It provides expertise in life science research, since many of the world leading pharmaceutical companies and some famous research institutes are located here. The main focus in the innovation centre is biotechnology, pharmacy, chemistry, and information technology. The people from different companies and institutions meet, for example in the InVento restaurant in the innovation centre, to talk and exchange information. The first biotech companies to move into the innovation centre were the newly started Actelion, Discovery Technologies, and Rolic. The Basler Kantonalbank provided financial support for building up laboratories and administration offices, which made the centre attractive. It currently has over 20 companies employing 600 people. The centre is a private company and is not sponsored by either public or industrial funds. In view of the space of 27,000 m^2, the Park Allschwil has become the second biggest innovation centre in Switzerland after the TechnoParc Zurich[233].

11.4.9 University technology transfer

11.4.9.1 Unitectra

Unitectra is a non-profit technology transfer organisation owned by the Universities of Bern and Zurich. Research results from the universities are transferred into products and the transfer occurs in collaboration with established companies or through creation of new start-up companies. In this case, a start-up company is a business arising directly from R&D conducted at a university. The technology transfer services support new start-up companies in their the first year with infrastructure, advice, and financing. Services also include commercialisation of research results involving intellectual property protection (e.g. patents), and training and education for scientists. The collaboration benefits both the universities and companies; the companies get access to top scientists for joint research, and a new job opportunity is created for the scientists[234].

11.4.9.2 Technology Transfer at the University of Basel

Since the major focus of the University is research, teaching, and services, the University finds significance in applying its research in the industrial and public sector. To do this, the University of Basel has its own Office of Technology Transfer (OTT). As with other technology transfer organisations, its purpose is to evaluate the commercial use of research

[233] Innovationcenter of North-West Switzerland, http://www.innovationszentrum.ch/About.htm.
[234] Unitectra, http://www.unitectra.ch/en/portrait/6.htm.

results, protect intellectual property, and transfer the results to the public sector or industry. The University of Basel also supports start-up companies by offering academic advice or workspace, instruments and assistance in establishing initial contact with business and venture capitalists for financial support[235].

11.5 Comparison of the four clusters

This chapter has sought to provide an overview of the cluster milieus focusing on the life science industry. Successful pharmaceutical clusters derive their competitive advantage from such factor conditions as financial support, skilled labour, infrastructure and related supporting industries, including collaboration between companies and research communities[236]. The results from the case study suggest that to be successful a life science cluster requires a satisfactory scientific base in high-level research. This is what differentiates the pharmaceutical industry from many others; it is a science-driven business, and therefore proximity to top universities is important. From this perspective, Massachusetts is in the lead due to top-level research at world-class universities, such as Harvard and MIT. In addition to the scientific base in Boston-Cambridge, the highly skilled workforce and daily interaction between industry and academia are important factor conditions in attracting big pharma.

Indeed Massachusetts has the most R&D units of the clusters in this study with 22 big pharma R&D units. Switzerland has 11, Ireland has eight and Singapore has eight big pharma R&D units. Within this industry, one of the main competitive advantages is having access to and building expertise in the biomedical sector. In this area, good is not enough; a lack of top talented scientists in the life science industry is a threat to the growth prospects of a cluster.

As noted earlier in this case study, many pharmaceutical companies rely on research institutions since they are an externality that has the potential to result in drug discoveries for commercialisation. Commonly, all universities in the clusters use technology transfer programmes. Most of the universities in the clusters have established joint venture research facilities for university-industry partnerships and exchange programmes. One common advantage of all businesses in these clusters is the high concentration of pharmaceutical companies in the region, access to top-class laboratories and

[235] Wissens-Und Technologie Transfer Uni Basel, http://pages.unibas.ch/wtt/TT-Philosophy/tt-philosophy.html.
[236] Porter, 1990.

the creation of networks (such as innovation centres) that foster partnerships between academia and industry.

Government policy is an important initiative in creating successful clusters[237]. Strong government leadership can help create the necessary conditions for pharmaceutical companies to grow. The core feature of the initiative is funding of basic research and scientific training. Every region has a unique set of local conditions that provide the economic basis upon which companies compete in a region. These economic foundations make capital available to support existing and new companies. Progress has been made by the Science Foundation Ireland (SFI) in attracting leading international companies to Ireland, including research scientists. The massive EUR 184 billion NDP plan 2007-2013, (of which EUR 6.1 billion will go to science, technology, and innovation) is central to the Irish goal of becoming a global knowledge-based economy. SFI has major opportunities to build and strengthen scientific research and benefit the long term competitiveness of Ireland. This in turn, can be an issue, since the economic development in Ireland is strongly government-led.

Massachusetts has the highest levels of NIH funding per biopharmaceutical employee in the US. The region received USD 2.27 billion in 2005, making it the most strongly government-supported cluster. But the NIH funding has levelled off markedly since 1998, and if the decline in funding continues, the conditions for R&D will become less favourable, even though a high level of private donations are also important sources of R&D funding. This could potentially affect the Massachusetts economy, since the enormous amount of funding leads to growth in the life science cluster. Government funding or public money for research provides a strong signal to private investors, since the government is committed to providing an attractive location for its investments. This can lead to private money following public money. Massachusetts and Switzerland receive a lot of venture capital. The life science cluster in Ireland has a target fund of EUR 25 million, but this is still a long way from the aggressive venture capital communities in Massachusetts and Switzerland. Singapore needs to develop its venture capital industry; this can be explained by it being in an early stage of development.

For most multinational companies, tax is an important criterion in the location decision[238]. Commonly, the clusters have or are updating their tax codes to make them more attractive to new companies and more competitive. For example, Singapore is to decrease its corporation tax rate

[237] Ibid.
[238] Ibid.

from 20% to 18% in 2008. If the Swiss Canton of Zug is excluded with its 17.8% corporate tax, this places Singapore in second place, after Ireland's 12.5% corporation tax rate. The remainder of Swiss provinces are over about 25%. Ireland is the best location for manufacturing operations, due in part to its previous *Manufacturing Rate of Corporation Tax* of 10%, remaining at 10% till 2010. This will increase to 12.5%, but still makes Ireland the best tax location for manufacturing units. This can be seen in our empirical data: Ireland has 40 manufacturing operations located in the country, while Switzerland has 20, Singapore 14 and Massachusetts 13. Massachusetts has the highest corporation tax rate both in the US and when comparing to the other clusters, but the *Single Sales Factor*, has significantly reduced the firms' state tax which means Massachusetts has become the most competitive state regarding state tax weight, especially for medium- sized and large companies as its taxation does not include property and payroll factors.

Singapore and Switzerland have the most effective and well-developed infrastructure. Such factors may seem trivial but are important factors in the light of the intense competition for top scientists, skilled employees and decision-makers.

To sum up, each of the regional clusters here emphasises a particular factor or factors which contributes to their success. Massachusetts has become a world leader in bio-pharmaceutical R&D, mainly due to its unique proximity to world-class academic institutions, major teaching hospitals and well-financed and aggressive venture capital communities. Ireland is attracting multinational companies mainly due to its low corporation tax rates. Singapore also attracts foreign pharmaceutical companies and pharmaceutical start-ups because of its tax incentives and its comprehensive air communications and local infrastructure which provide a flow of goods and services to markets around the world. The company-friendly infrastructure increases the competitiveness of Switzerland. Furthermore, Swiss taxes are relatively low and the international business community is well-developed with agile financial support.

12 The Shift to Asia[λ]

The industrial move to Asia started as an opportunity to gain cost advantages by producing in low wage countries. As Asian economies have grown, the educational system has improved and industrial capabilities have increased. The operations of multinational companies in Asia have also expanded to include R&D and more advanced manufacturing. In the case of the pharmaceutical industry, this shift has mainly been focused on China, then India and now many of the big pharmaceutical companies are establishing themselves in Singapore. After the establishment of manufacturing units, clinical trials used the potential of the enormous populations in China and India, followed by R&D units taking advantage of the large group of highly skilled and educated scientists.

The new localisations in Asia are not only dependent on the lower wages of the workforce, but also other economic incentives such as lower taxes and subsidiaries. Furthermore, China and India are particularly huge markets with a low degree of penetration, showing potential to become two of the most important future markets for pharmaceutical companies. However, localisation in Asia is not always unproblematic for Western companies; for example the infrastructure is generally behind, the culture is different and competition from generics is significant.[239]

Linked to the (legitimate and illegitimate) competition from generic drugs is the issue of protecting intellectual property, which in many cases is either far behind the Western laws or is not enforced properly. However, this problem has been recognised and both China and India are making efforts to improve this. Singapore, with its stricter laws, is an interesting location in this regard.

In the following sections, a SWOT-analysis of China and India will be conducted, followed by a concluding comparison between the two as locations for foreign pharmaceutical companies. The SWOT analysis will be implicitly based on Porter's theories of the determinants of national advantage, with a more explicit division of the identified conditions in the subsequent comparison of China and India.

[239] PriceWatherhouseCoopers, November 2007, http://www.pwc.com/Extweb/pwcpublications.nsf/docid/21B2F49330AAF759CA257316002CDCD4/$file/Asiapharma.pdf.

12.1 China

The Chinese economy has undergone tremendous growth in recent decades, keeping an average annual growth of 9.8% between 1993 and 2005[240]. However, this magnificent growth has also brought on a colossal problem, the Chinese environment is severely damaged and land and water are badly polluted. Also, economic growth is not evenly distributed within the country. The coastal areas are driving the growth whilst inland is lagging behind in many aspects. The economy is growing, maybe at risk of overheating, and foreign investments are increasing. For foreign companies, China has mostly been a manufacturing hub, mainly because of low wages and an abundant workforce.

This has been true of the pharmaceutical industry as well. During the last 10 years, China has been established as an important location for R&D operations as well, first for clinical trials, because of the large population, low wages and large market potential. Thereafter, research units were established to harness the potential of the highly educated Chinese workforce.

The Chinese healthcare market was worth about USD 35 billion in 2004, and expected to grow rapidly to around USD 350 billion in 2025. This quick growth is fuelled by the growing Chinese middle class and general economic growth.[241]

Except for the international pharmaceutical companies established in China, there are also a large number of domestic actors on the market. These companies are private as well as state-owned enterprises. Generally, the Chinese companies are not as R&D-intensive as the giants, therefore being forced to focus to a higher extent on generic drugs. The drugs produced by Chinese enterprises are to 98% generic drugs, and many of these drugs are patent-protected[242].

The standard corporation tax in China is currently 33%. However, for foreign enterprises located in the coastal cities, this is reduced to 24% and for foreign enterprises located in special Economic Development Zones the tax is reduced to 15% to stimulate growth at those locations. Still, these

[240] Deutsche Bank Research. 2005. 'China lifts annual growth figures', 2006, http://news.bbc.co.uk/2/hi/business/4594132.stm.
[241] McKinsey & Company, http://www.mckinseyquarterly.com/article_page.aspx?ar=1798&L2=7&L3=10
[242] Capie, 2007, pp. 98–105.

taxes may be subject to future change, since there has been discussion of a flat rate of 25% tax. [243]

12.1.1 Strengths

Among the most important strengths of China is its population. The population provides industry with an abundant workforce. Even though the general degree of education is quite low, the sheer size of the population ensures a huge amount of highly educated and skilled professionals. For example, China is second only to the US when it comes to the number of R&D researchers, totalling over 800,000 (2004).[244] As an added value to this gigantic workforce the wages are lower than in OECD, giving China a clear cost advantage, especially in labour-intensive manufacturing.

There are also several centres of scientific excellence in China, in the form of universities and technology parks at high international level. Chinese companies and institutions have also developed specialist competences in areas of interest to foreign pharmaceutical companies, such as gene therapy, stem cell research and modernisation of traditional Chinese medicine.[245]

An effect of the large population and lower wages is favourable opportunities to conduct clinical trials in China. Not only because of the wide range of trial participants, but also the large and rapidly growing market, one of the decisive factors in choosing the location of clinical trials. [246]

China is currently far ahead of India in foreign direct investment, largely due to more effective legislation in this regard. The government has changed the laws and policy from being restrictive and only allowing foreign investment in approved joint ventures with domestic companies, to allowing free foreign investment. [247] In 2004, China attracted over USD 60 billion in foreign direct investment[248].

12.1.2 Weaknesses

The Chinese legislative system has put a lot of work into setting up new laws to protect intellectual property rights. Since joining the world trade organisation (WTO) in 1999, Chinese law has been updated to comply with

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[243] *Overview of PRC taxation system*, http://www.pwchk.com/home/eng/prctax_corp_overview_taxation.html
[244] Zeng & Wang, 2007.
[245] Liu & Lundin, 2006.
[245] Liu & Lundin, 2006.
[246] Ibid.
[247] Zeng & Wang, 2007.
[248] UNCTAD, 2005.

WTO standards, an important cornerstone of promoting commercialisation of science and innovation and trade in general. However, so far these laws have not been enforced, making them merely empty threats. This is an important area that needs improvement in order to stimulate R&D within the pharmaceutical industry in China, which is highly dependent on patents and intellectual property protection. [249]

The previously mentioned issue is linked to the low level of R&D spending in China. For example, China spends 1.23% of GNP (2004) compared with the US, Japan and Germany which spend over twice that figure. Furthermore in a similar comparison, publication in scientific or technical journals in China is 30-40 times lower per capita than that of the US, Japan and Germany. As for the domestic Chinese pharmaceutical industry, R&D spending is low and innovation is also low. This could be seen as both a reason for and a consequence of the domination of generic drugs on the Chinese market.[250]

Even though a great number of Chinese attend and complete tertiary education, the general education level is still low, especially in the rural areas. This is one reason for the increasing gap between the regions experiencing high growth and increased prosperity and the regions with limited growth.

Furthermore, the Chinese banking system is not working in an efficient way. The Chinese banks have been granting big loans to state-owned enterprises which in many cases cannot repay them[251]. Currently, the interest on savings accounts is lower than the inflation rate which means those Chinese lending money to the banks are making a real loss. This has created a grey market for loans at higher interest rates. The money from this business is then loaned to private companies at a high interest rate. To work more efficiently, the "real" banks will need a higher interest rate to attract Chinese savers and be able to lend money to private enterprise. As a result of this problem, the availability of venture capital is generally low in China today[252]. This issue is further worsened by the previously mentioned lack of intellectual property protection, since innovation this in order to provide returns on investment in new high-tech business ventures[253]. With major uncertainty about opportunities for getting a return on venture capital investment, the market for providing venture capital becomes unattractive.

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[249] Maskus, Dougherty & Mertha, 1998.
[250] Zeng & Wang, 2007.
[251] 'The Leak In China's Banking System', 2004, http://www.businessweek.com/magazine/content/04_46/b3908048.htm
[252] Zeng & Wang, 2007.
[253] Maskus, Dougherty & Mertha, 1998.

12.1.3 Opportunities

China's market is large and rapidly growing; one important reason for companies to establish in China. Growth in the pharmaceutical market is partly driven by overall economic growth, but also by the rapidly growing Chinese middle class with money to spend on healthcare. According to Qin et al, economic growth is also important since it is driving demand for investment in China[254].

Another opportunity for China to attract foreign direct investment is its lower tax for investments in certain economic development zones. These economic advantages may be driving investments in these areas but they may yet change and not remain as a perpetual incentive to stay in China.

Tougher enforcement of the new intellectual property protection laws are needed in order to stimulate investment in manufacturing as well as to a greater extent in R&D operations. According to this study, it is evident that since these laws were implemented, R&D investment by big pharmaceutical companies in China has risen, although the new laws are not the sole reason for this. These laws are not only enforced for foreign pharmaceutical companies, but also help create a favourable environment for domestic research-intensive companies.[255]

Also, better access to venture capital is needed to improve the economic environment for new innovative firms. An important part in creating this is improving the banking sector to use capital more efficiently.[256]

To increase the employee competence needed in a technology-intensive industry requires a restructuring of the education system. Compulsory schooling needs to be improved and needs to reach the rural areas, not just the coastal cities. With improved tertiary education, this can provide an even greater workforce for the pharmaceutical industry.

12.1.4 Threats

The Chinese economy is showing a high inflation rate, far above the government goal of 3% - the actual rate in November was around 6.5%[257]. This has happened despite five recent interest rate raises by the Chinese Central Bank. An overheating economy may create excess demand for

[254] Qinet al., 2006, pp. 751–774.
[255] Maskus, Dougherty & Mertha, 1998.
[256] Zeng & Wang, 2007.
[257] 'China's inflation rate hits 11-year high', 2007, http://money.cnn.com/2007/11/13/news/international/china_inflation.ap/index.htm?section=money_news_international.

goods and thwart investment in China. However, whether China is overheating or not is something about which economists disagree.

A global competitive environment is bringing new challenges to China. As wages in China rise, so one of its comparative advantages diminishes and creates opportunities for competition from other countries with lower wages. India is also on the rise as a competitor to China with a huge workforce which may also have higher levels of competence. A risk here is a lack of domestic innovation in China causing dependence on foreign innovation.[258]

Chinese society is becoming increasingly divided into urban and rural areas, in regard to such things as wage levels, education and foreign investments. This gap threatens to destabilise society and to decrease growth in the longer term.[259]

A huge challenge for China is the destruction of the environment and the need for a change in attitude to it. According to the World Watch Institute, 16 of the world's 20 most polluted cities are in China and this situation is not likely to improve in the next few years. This is partly due to the Chinese reliance on coal-powered electrical plants. Furthermore, the rivers in China which provide much of the fresh water are also heavily polluted, creating a shortage of clean water.

The huge generics market is a challenge, not to China as a country, but to foreign companies establishing themselves there and trying to gain a share of the pharmaceutical market. Competing with this requires lower prices, which means lower margins.

12.2 India

Much like China, India was industrialised in the 1950s and was then an economy dominated by state-owned companies. India has not been able to keep up with the extraordinary Chinese growth, but is still making a good showing with average 6% growth since 1980. This figure has seen an increase during the 21st Century as the Indian economy has grown by over 9% for the last two years.[260]

However, where China has had a clear focus on manufacturing, India has had a larger focus on the service and IT sectors. For example, a large number of companies have outsourced their call centres to India in recent decades. A study conducted by Deutsche Bank concludes that domestic

[258] Zeng & Wang, 2007.
[259] Ibid.
[260] Srinivasan, 2004, pp. 613-636. Deutsche Bank Research, 2005.

Indian companies are generally better managed than their Chinese competitors[261]. The Indian pharmaceutical industry is similar to the Chinese, with a focus on manufacturing, but some R&D operations have also established in the last 10 years. Furthermore, the Indian pharmaceutical industry has more extensive biotechnological operations. Generally, the Indian pharmaceutical companies are larger than their Chinese counterparts, with a few of them ranked just outside the top 50 by revenues.

As in China, the development in India has gone from only accommodating manufacturing by multinational pharmaceutical firms, to also including R&D operations in a number of locations. The domestic firms control about two thirds of the market, which is largely due to the domination of generics and to some extent contract manufacturing on the Indian market. In India, there is major emphasis on being at the forefront in developing the first generic biopharmaceuticals[262].

India has several universities known around the world and over half a million students graduate each year in biotechnology, bioinformatics and biological sciences. Indian scientists also has an advantage over their Chinese counterparts due to the higher level of English afforded them by India's colonial history. Even though India has spikes in its educational level, it also faces some of the same problems as China as the educational level is significantly lower in the rural areas.[263]

The barriers of entry to the Indian pharmaceutical market are relatively low. This has made the industry fragmented and created many minor players and a higher cost of competition. This may decrease with the recent introduction of new patenting laws. Another aspect of the cost competition is the price regulation set up by the government. Drug prices are set by The NPPA (National Pharma Pricing Authority) which lowers the profit margins of pharmaceutical companies. [264]

The tax rate in India is 30% for a domestic company and 40% for a foreign company. The Indian government has formulated a strategy, mainly in biotechnology, for attracting foreign direct investment. It relies on economic incentives such as lower tax or even no tax for a limited period. Foreign investments in India have increased during the last decade, however China

[261] Deutsche Bank Research, 2005.
[262] Sandström, 2007, [Personal communication].
[263] Swedish Trade Council, New Delhi, 2005.
[264] *Indian pharma Industry: SWOT analysis*, 2004, http://www.equitymaster.com/DETAIL.ASP?story=5&date=6/21/2004.

is still far ahead in that aspect.[265]

12.2.1 Strengths

What originally made companies outsource operations or establish themselves in India are the low production costs. Production in India is generally about half as dear as producing within the OECD and sometimes even less, which is a major cost advantage in price-sensitive industries[266].

India currently has the largest group of English speaking scientists outside the US. India has some very well-respected universities and a huge amount of students in tertiary education. The Indian universities have created a large, well-educated workforce. Even though the level of education in India is not top-class compared to the world leaders, it is improving and has major potential for improvement[267].

Historically, there have been better returns on investment in India than in China[268]. Logically this should spur a higher rate of foreign direct investments and availability of venture capital. Even if the availability of venture capital is higher than in China and the banking system is functioning more efficiently, there is still some way to go before it reaches the same level as many of the OECD countries.

Strength in developing a manufacturing base is being able to deliver high quality products. An indication of this can be seen in the level of Indian manufacturing plants. For example, India has the largest number of FDA-approved (US Food and Drug Administration) plants outside the US.

12.2.2 Weaknesses

India is still far behind the West in its level of infrastructure. In the rural areas, electricity and clean water may be scare commodities[269]. This is an issue since a company may have to build up this infrastructure themselves when establishing a new facility, thus decreasing the cost advantage of the

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[265] Swedish Trade Council, New Delhi, 2005.
[263] *Entry Strategies for Foreign Investors*, http://siadipp.nic.in/policy/entry.htm; UNCTAD, 2005.
[266] *Indian pharma Industry: SWOT analysis*, 21 June 2004. Equitymaster. retrieved 28 November 2007, http://www.equitymaster.com/DETAIL.ASP?story=5&date=6/21/2004. "Advantage Crams." 2006. http://www.expresspharmaonline.com/20060615/market01.shtml.
[267] Dahlman & Utz, 2005. http://info.worldbank.org/etools/docs/library/145261/India_KE_Overview.pdf
[268] Srinavasan, 2006.
[269] Deutsche Bank Research, 2005.; "China and India: The race to growth." http://www.mckinseyquarterly.com/article_page.aspx?ar=1487&l2=16.

location. To further stimulate growth, some state-owned assets may need to be sold and the money invested in infrastructural improvements[270].

Indian labour laws are quite rigid and the trade unions are powerful. The laws were made when India was still a socialist state with government-owned factories. For example, a company with over 100 employees cannot fire them without government approval. This creates a rather rigid labour market. According to Kundra, this adds cost to production in India and decreases the cost advantage[271].[272]

12.2.3 Opportunities

Like China, India has had weak intellectual property protection. Previously, a product could not be patented. What could be patented was the process so, long as a product could be produced in a slightly different way, patents could be sidestepped. Today, India has adapted intellectual property protection as stipulated by the World Trade Organisation, and since 2005 products can now also be protected by patents.[273] This new intellectual property protection, coupled with increased efforts to enforce the laws, now provides even better growth opportunities. According to Gould and Gruben, strong intellectual property protection is better for economic growth[274]. Furthermore, stronger protection can increase margins for multinational companies and increase the focus on R&D for domestic players[275]. The domestic Indian companies have better developed R&D and have moved away from the generics focus to a larger extent than the domestic Chinese pharmaceutical companies[276].

Today India is focusing on biopharmaceutical generics[277]. Groundwork is under way to provide an opportunity to start exploiting the end of the first biopharmaceutical patents. However, this is more challenging than regular generic production. If this investment succeeds, it will give India a leading role in this future market. Biotechnological production lines are generally more complex than regular chemical ones, which makes success less certain. However, there is no doubt that the market has great potential.

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[270] Srinavasan, 2006.
[271] Kundra, 2003, http://www.hinduonnet.com/thehindu/biz/2003/06/02/stories/2003060200100200.htm
[272] Srinavasan, 2006.
[273] Swedish Trade Council, New Delhi, 2005.; Srinavasan, 2006.
[274] Gould & Gruben, 1996, pp. 323-350.
[275] *Indian pharma Industry: SWOT analysis*, 2004, http://www.equitymaster.com/DETAIL.ASP?story=5&date=6/21/2004.
[276] PriceWatherhouseCoopers, http://www.pwc.com/Extweb/pwcpublications.nsf/docid/21B2F49330AAF759CA257316002CDCD4/$file/Asiapharma.pdf.
[277] Sandström, 2007, [Personal communication].

As in China, the Indian middle class is growing and with it the ability to buy pharmaceuticals. The more money spent on pharmaceuticals, the more favourable the conditions for brand name drugs, which cannot compete with generics in a market with a high price focus.

Major government funded R&D programmes have been initiated in India to improve its scientific output. These programmes are ambitious and will triple the R&D spending 2004-2007 to 2% of GNP. The goal is to build up a strong knowledge-based economy. Current R&D spending is low compared to OECD, but India is trying to catch up with the West and the introduction of stronger intellectual property protection will likely encourage larger R&D investment from domestic and international companies.[278]

12.2.4 Threats

The Indian economy is less integrated than the Chinese one in the world economy. This may be due to more restrictive laws on foreign investments and import of goods. Such protectionism could threaten the economic growth as linked to this are strict labour laws which could scare off foreign investors. [279]

Currently India faces the threat of an HIV/AIDS epidemic, an epidemic which is having its worst effects in the most prosperous parts of the country. This could prove a social and economic disaster, halting the growth of the Indian knowledge-intensive industry.[280] Currently around 2-3.6 million Indians are infected with HIV and another 125,000 have AIDS.[281] According to the United Nations Development Programme, the impact of AIDS will slow the economic growth in India by almost one percentage point in India by 2019.[282]

In India, though not as much as in China, there is major competition from generic drugs. This may be a threat to some of the big pharmaceutical companies and in the long run may force an industry-wide focus on price pressure.

12.3 Comparison of China and India

This comparison of China and India will be guided by Porter's determinants of national advantage.

[278] Schoen, 2005.
[279] Srinavasan, 2006.
[280] Ibid.
[281] *HIV and AIDS in India*, http://www.avert.org/aidsindia.htm.
[282] United Nations Development Programme, 2006, http://www.undp.org.in/.

12.3.1 Factor conditions

Firstly, a main difference in the economic and social environments is that India is the largest democracy in the world, whereas China is a single-party Communist state. The Indian market is a market economy, albeit regulated, while the Chinese government is striving for a socialist market economy with state-owned and private companies competing freely. The Indian market has government-regulated pricing for pharmaceuticals and much stricter labour laws than the Chinese market. An issue for large multinational companies is the strong labour unions in India whereas in China, where the labour unions are weaker, the state or government has a stronger influence.

China and India share many characteristics as fast-growing economies and markets with huge populations. These characteristics are probably also the most important drivers for establishing in China or India. The populations comprise large groups of highly educated and skilled professional, but also enormous inequalities in education and income, especially between urban and rural areas. One advantage for India in this respect is the number of English speakers.

They share advantages and also some problems. Perhaps the most important of these for the patent and research-dependent pharmaceutical industry is the issue of intellectual property protection. Both countries have recently implemented new laws in line with World Trade Organization standards. However, in China these laws are not enforced and in India it is too early to tell what effect the new laws will have. What is certain is that the former weak protection has spawned a problem of counterfeit drugs for the pharmaceutical industry. There is also competition on the domestic market from cheaper generic drugs. Especially in India, there is currently a major focus on producing generic biopharmaceutical drugs in the near future.

Both countries also face major social problems. In India, an HIV/AIDS epidemic is spreading, especially in the most prosperous parts. Meanwhile in China, the environment is suffering, and swift action is needed to slow this down and hopefully turn it around.

According to a report by A.T. Kearney, China is currently the most attractive location for clinical trials outside the US, followed by India in second place with similar rankings across the categories. China has an advantage in relevant expertise and India has one in regulatory conditions.

Both China and India are showing a clear low cost advantage compared to the US.[283]

12.3.2 Demand conditions

Both China and India have large and fast-growing middle classes creating a growth in the pharmaceutical industry. The domestic market is largely satisfied by generic drugs, which are manufactured by local companies. However as the middle class grows, an increase in sales of regular, more expensive pharmaceuticals could be expected.

12.3.3 Related and supporting industries

China is currently ahead of India when it comes to foreign direct investments, but investments in India are increasing. In regard to spurring domestic innovation in the pharmaceutical sector, India is ahead partly because of greater availability of venture capital for new companies. Also the Chinese banking system is facing trouble with bad debts, high inflation and inefficient use of capital. Innovation in domestic enterprises is generally rather low in the pharmaceutical sector, especially in China.

12.3.4 Firm strategy, structure and rivalry

The strategy of foreign firms establishing in China has generally been to manufacture at lower cost in China, and sell the goods outside of China, often in the US or Europe. With an increased educational level and R&D presence this is changing somewhat and more operations are being conducted in China and India. The growing domestic market in both countries is changing the strategy somewhat, making companies locate in China and India to gain access to these markets.

The source of pharmaceutical industry advantage is generally described as being in discovery and development of innovative drugs. In China and India, with lower wages and pharmaceutical spending per capita than in the Western world, the low-cost dimension is also an important factor, thus providing an advantage for generic drugs.

Currently, a larger number of big pharma companies have operations in China than in India. Of the ten largest big pharma companies, all have a presence in both China and India. Moving down the list, the presence in India is first to decrease followed by that in China. There are 58 units in China (14 R&D and 44 manufacturing units) and 42 units in India (9 R&D and 33 manufacturing). As shown by these numbers, the relationship

[283] Bailey, Cruickshank & Sharma, http://atkearney.com/shared_res/pdf/Make_Your_Move_S.pdf.

between manufacturing and R&D units is roughly the same in both countries, with manufacturing making up the majority of units.

13 Discussion

13.1 The future

In this study, we have identified and analysed the geography of big pharma R&D and manufacturing units. The general pattern shows a clear movement toward Asia. Indeed, the analyses show that nations such as India and China and clusters such as Singapore have the potential to compete for location of big pharma activity. Furthermore, the increasing importance of molecular biology has changed and will further change the pharmaceutical industry.

13.1.1 Technology

In this paper it has been envisaged that the revolution in molecular biology has had consequences for big pharma and the pharmaceutical industry. Some of these effects are known - such as the introduction of special biopharmaceutical firms in the industry – whereas other effects remain unknown. In particular, there is disagreement on whether big pharma *has successfully adjusted* its business to face this new industry landscape.[284] Furthermore, there is disagreement on the exact *character* of this adjustment.

Indeed, we know from our empirical study that both research and manufacturing activities involve biotech applications. Furthermore there have been many accounts regarding acquisitions of and collaborations with biotech firms. We also know that many big pharma R&D units are located at places where biotech innovation is at the forefront. In that sense, it is known that big pharma has at least reacted to the applications of biotechnology.

Whether or not these adjustments should be considered successful naturally lies in the specific criteria for use of a successful company. Concerns may be raised if success is measured by numbers of pipelined pharmaceuticals. However, some point to the fact that such measures do not truly capture the *innovativeness* of big pharma and that these firms are indeed successful (or at least not *less* successful than before)[285]. Others cite declining numbers of pharmaceuticals from in-house R&D as evidence of a change in the business concept of big pharma[286]. This change makes big pharma less vertically

[284] Cooper, Sinskey & Finkelstein, 2002.
[285] Schmid & Smith**,** 2005.
[286] Cooke, 2004a.

integrated and more specialised on contracting and marketing pharmaceuticals from the research leading biotech companies.

In our view, the future of big pharma in its current form is contested. In the knowledge-intensive pharmaceutical industry it is imperative to discover drugs in-house and big pharma is failing, as can be seen from the increased reliance on findings within smaller biotech companies.

13.1.2 The shift towards Asia

From what can be seen through our empirical study, Asia is becoming a key player in the global pharmaceutical industry. By now, the Asian formula of pharma success is familiar. It consists of a low-cost manufacturing base joined with a considerable pool of highly skilled workforce. The leading Asian countries are Singapore, China, and India. These countries attract multinational pharmaceutical companies by offering savings on R&D costs, low taxes, grants, and infrastructure support. Some companies, like Schering-Plough, choose Singapore as their manufacturing and R&D hub in Asia, mainly due to the rules for intellectual property protection. Others choose China and India due to their large populations and the focus on generic manufacturing in the domestic life science industries[287]. The three leading countries in Asia provide off-shoring opportunities across all phases of the innovation value chain and all are gambling on new skills and resources continuing to come. A common weakness of India and China is intellectual property protection which may be holding back the degree of innovation and product development of multinational companies. As can be seen in our empirical data, China has 14 R&D operations and 44 manufacturing units, while India has 9 R&D operations and 33 manufacturing units. Despite the enormous differences in size of the countries, Singapore also has 33 manufacturing operations and 9 R&D units. It is plain that companies in Asia are establishing themselves as manufacturing hubs.

13.2 Reflections

This paper has been dedicated to unravelling, analysing and explaining the geography of big pharma R&D and manufacturing activities. Naturally, the explanations rely on the extent to which such a geography could be determined. As already stated, it has been difficult to obtain values for parameters such as workforce and investments from these corporations. Furthermore, the number of discontinued plants has been low. Such

[287] Vassilieva, 2007, http://www.pwc.com/extweb/ncinthenews.nsf/docid/13CC1A82ED77DF15CA25733000135AD0

information would have improved the analysis considerably, adding a size dimension to the units rather than just a number.

The analysis has attempted to explain the geography of big pharma by drawing on theories and other accounts. Naturally, no single factor can explain the location of big pharma R&D and manufacturing operations. Rather, location is the result of actions of interrelating actors on different geographical levels. On the one hand, location can be understood in the characteristics of the pharmaceutical industry, such as changes in technologies and the attractiveness of different nations. On the other, every individual location is related to the state of the specific firm. Furthermore, many units were located at a time when the pharmaceutical industry was different from what it is today.

13.3 Further Studies

In this study, a number of subjects suitable for further research have been identified. Firstly, it would be useful to have a study focusing on the details of the units such as some account of size and specific operations. However, to find these details would require successful contact with important information sources within the companies or by using government statistical databases. According to our knowledge, both of these information resources are problematic to use. This type of information should indeed be available to the companies themselves, but with no any obvious gain to be made by giving it out, companies hold onto it. As for the other source of information, government statistical databases, there are considerable differences between the way in which information is presented and the amount of information companies are required to publicise. Since big pharma geography is global, a lot of effort would be required to find some adequate way of harmonising such information.

This master's thesis has given accounts of the increased network structure of the pharmaceutical industry. Thus, one relevant study would be to include the various collaborations between the actors in the pharmaceutical industry. Such a study would possibly be even more difficult to complete satisfactorily because such network ties do not necessarily have any visible impact on the environment. This could include trying to establish a relationship between localisation of smaller pharmaceutical companies and big pharma.

14 Conclusion

This master's thesis was dedicated to the *identification*, *presentation* and *analysis* of big pharma R&D and manufacturing units. These combined undertakings have resulted in many insights into the global geography of big pharma. Some of these can be obtained "directly" from the empirical study whereas others are drawn from the analysis. These insights include:

- There is a decrease in big pharma presence in Puerto Rico, a centre of manufacturing, and in Japan. Furthermore, a number of the largest pharmaceutical companies are closing plants in favour of an outsourcing solution.
- The localisations during the last 10 years seem to be well in line with the ideal company as proposed by NERA Economic Consulting[288]. This indicates that recent localisation decisions seem to be driven to a lesser extent by historical factors and more by rational reasons.
- In analysing the data collected in the empirical study, evidence of areas with high concentrations of big pharma activity can be found, known as clusters. These clusters have emerged from different backgrounds and developed into entities with different characteristics, such as focusing on manufacturing or R&D. Not surprisingly, the major pharmaceutical industry clusters are found in industrialised countries and often in connection with an extensive pool of knowledge and competence in the field, especially for R&D operations.
- To some extent, the big pharma geography of R&D units in Europe can be understood in light of the character of technological change and the strategies of TNCs and nation-states. More specifically, the revolution in molecular biology seems to have had some impact on the big pharma geography especially in the UK and France.
- Certain dynamics in the localisation of big pharma can be observed. For example, the location decisions made today differ from those made 20 years ago. Considering the new establishments in the last 10 years, a movement of big pharma operations towards Asia can be seen, especially towards Singapore and the fast-growing markets of China and India. Not only are China and India possible locations for low-cost operations – with their huge populations and rapid economic growth they are developing towards becoming a very important market for the pharmaceutical industry.

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Corporate Information

Except the above stated sources, the information for the empirical study was mainly compiled from published corporate information from the 50 companies (see Delimitations, for details). The main sources were corporate websites, annual reports or forms 20F and 10-K.

Pfizer	Abbott Labs	Novo Nordisk	Altana (Nycomed)	Watson
GlaxoSmith Kline	Roche	Eisai	Chugai	Biogen Idec
Sanofi Aventis	Amgen	Teva	Solvay	Shire
Novartis	Boehringer-Ingelheim	Merck KGaA	UCB Group	Shionogi
AstraZeneca	Takeda	Sankyo	Genzyme	Seiyaku
Johnson&Johnson	Astellas	Otsuka	Serono	King
Merck	Schering-Plough	Forest Labs	Allergan	Tanabe
Wyeth	Bayer	Daiichi	Mitsubishi	Seiyaku
Bristol-Myers	Schering AG	Baxter	Gilead Science	Kyowa Hakko
Squibb	Genentech	Akzo Nobel	Lundbeck	Mylan Labs
Eli Lilly				MedImmune
				Ono

16 Appendix: The Empirical Study

The empirical study is too large to be attached to this paper. However it is available in electronic form, preferably by contacting the authors:

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03 Sammanfattning - Användningsdriven utveckling av IT i arbetslivet - Effektvärdering av tjugo års forskning och utveckling kring arbetslivets användning av IT. *Brief version of VA 2007:02, for brief version in English see VA 2007:13*

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