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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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Abstract

Looking over the Shoulders of Giants - A study of the geography of big pharma R&D and manufacturing operations

Jonas Timsjö

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 with this master's thesis is to identify this unknown geographical configuration of big pharma R&D and manufacturing units. By analysing these empirical data areas with high concentrations of big pharma activity and trends in localizations can be identified. Following this, analyses from different perspectives have been carried out to explain certain aspects of these localizations and trends. In order to achieve this, a database of the units was constructed. Information was primarily based on corporate information sources and secondarily based on other sources such as online newspapers and industry studies. The study was limited to only include 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, so called 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 localization can be observed. In general 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 larger extent than R&D by cost optimization, such as taxes, labour costs, and economic incentives.

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Populärvetenskaplig sammanfattning

De faktorer som styr lokaliseringen av F&U (Forskning och Utveckling) -enheter och produktionsenheter för stora läkemedelsföretag – big pharma – är i stor utsträckning *kända*. Den exakta geografiska fördelningen av F&U- och produktionsenheter är emellertid *okänd*. Det är denna okända fördelning som den här uppsatsen har haft som syfte att klarlägga genom att kartlägga de 50 största läkemedelsföretagens F&U- och produktionsenheter. Information har främst inhämtats från företagen själva via webbsidor och årsrapporter.

Den resulterande geografin visar att de flesta produktions- och F&U-enheterna finns i USA, Europa och Japan. Lokaliseringen av produktionsenheterna har emellertid en större spridning där länder som Kina, Indien och Brasilien också är tongivande. Både F&U- och produktionsenheter förekommer i agglomerationer. De områden där flest F&U-enheter finns är USA: Boston och San Francisco/San Diego, Europa: Paris och London och Japan: Tokyo och Osaka. De områden där flest produktionsenheter är lokaliserad är Amerika: Boston, Puerto Rico och Mexico City, Europa: Dublin och Bern samt Japan: Osaka och Tokyo. De senaste åren har den största ökningen av enheter skett i Kina, Indien och Singapore.

Det har varit omöjligt att göra en *komplett* analys av dessa resultat. Därför har vi valt att göra några nedslag i de trender och mönster våra resultat uppvisat. En analys har ställt den *ideala* lokaliseringen av enheter i relation till våra resultat. Den ideala lokaliseringen avser här lokaliseringen av enheter som några tongivande personer vid ett antal big pharmas hade beslutat sig för om de kunnat ”börja om från början”. En annan analys har jämfört lokalisering av F&U-enheter i relation till starka fästen för bioteknologisk forskning över tid. En tredje analys har fokuserat på F&U kluster i Massachusetts, Ireland, Singapore och Schweiz. Slutligen har en SWOT (Strenght-Weakness-Opportunity-Threats) -analys av Indien och Kina genomförts.

Sammanfattningsvis kan man säga att dessa analyser förstärker den redan befintliga bilden av drivkrafter kring lokalisering av F&U- och produktionsenheter för stora läkemedelsföretag. F&U-enheter förläggs i hög utsträckning i anslutning till så kallade kluster där den vetenskapliga kompetensen är hög. Lokaliseringen av produktionsenheter drivs i större utsträckning av kostminimerande strategier vilket ger högre koncentrationer i regioner med låga skatter och låga löner.

Looking over the Shoulders of Giants

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

Preface

This master's thesis is a Bio-Entrepreneurship-Team-project (BET-project) written for Vinnova, the Swedish Governmental Agency for Innovation Systems, and UBE - 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 1.2.1 and at the end of the Table of Contents.

We would like to take the opportunity to warmly thank everyone that in one way or another has taken part in the process of this master's thesis.

Especially, we would like to thank Anna Sandström, supervisor at Vinnova, and Bo Norrman, supervisor at UBE, for letting us 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, January 10, 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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Notes on individual chapters

The symbols included on some of the chapter listings are used to clarify the individually written parts. Each symbol indicates the actual chapter and any subtitles that have been written by the author. The symbols correspond to the following authors:

- λ Johan Lindman
- θ Jonas Timsjö
- Ω Nancy Özbek

For further information please refer to chapter 1.2.1.

List of Figures

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 *Organization 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 has been appreciated 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 $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 to explain many of the previous unknown mechanisms of drugs. Indeed, ever increasing investments are put into R&D as to ensure that the *pipeline*[4] is full with drugs.

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

There are several, both academic[6], governmental/policy[7] and commercial[8], accounts 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 that relate to the availability of skilled scientists, 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 requirement 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 the identification, presentation and analysis of such a (global) geography.

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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)

1.1 Purpose and research question

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

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 include definitions of key concepts such as big pharma, manufacturing and R&D.
- How is this area of study going to be identified? To answer this question decisions has 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 with regards to dynamics. The purpose with this section is to answer questions of the following nature:

- Where are there large concentrations of big pharma R&D and manufacturing activity?
- 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, to the extent 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 *interesting regions (as suggested by our results)*, different *theoretical standpoints,* and a comparison with other *accounts in literature*.

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

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

1.2 Outline

In *Chapter 1*, the current chapter, an introduction to the paper is given stating the purpose, research questions, delimitations, and definitions. This is followed by:

- *Chapter 2* identifies and defines the field of the study.
- *Chapter 3*. In this chapter the pharmaceutical industry is briefly described to give the reader a basic comprehension of the pharmaceutical industry, the drug development process, the history, and some accounts on the future of the industry.
- *Chapter 4* is explaining the methodology used to determine the geography of big pharma R&D and manufacturing units.
- *Chapter 5* is giving a summarized view of the empirical study on big pharma localizations, in figures and text.
- *Chapter 6* is highlighting 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*. In this part a comparison between the findings of the empirical study and an industry idea of the ideal pharmaceutical company is conducted.
- *Chapter 9* is introduces a specific theoretical framework which is used to study the geography of big pharma R&D in Europe.
- *Chapter 10* is giving an overview of reasoning around localization for the pharmaceutical industry, including examples from the empirical study.
- *Chapter 11* consists of a description and comparison of four leading biopharmaceutical clusters.
- *Chapter 12* is analysing 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*. This chapter summarizes 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 sake these parts have been marked with a symbol representing the author: Johan Lindman (λ), Jonas Timsjö (θ) and Nancy Özbek (Ω). Chapters lacking symbols have been co-written.

1. Introduction
2. Identification
3. Background
4. Method
5. Empirical Data
6. Trends in Big Pharma Localization - λ
7. Location Theory
   7.1 - θ

7.2 - 7.33- λ
7.4 - Ω
7.5 - λ

8. Localization 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 contains the identification of the field for this study; including delimitations, definitions and background information. This is provided to set the study in its 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 units and R&D units, relating to human pharmaceuticals and vaccines. This is further developed in chapter 3 Method.

2.1 Definitions

Below follow some definitions of importance for this study.

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 generally no distinction between research and development is made, even though they differ from each other in reality. *Clinical trials* have not been included in this study, likewise production of pharmaceuticals exclusively for clinical trials have 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) medicine.
  (Drugs that can be bought without prescription)
- Veterinary pharmaceuticals.
  (Animal medicines)
- Generic drugs
  (Drugs that mimic pre-existent (ethical or OTC) drugs with patents expired)

[9] Ethical drug is a synonym for prescription drug that is often favoured by pharmaceutical companies despite being less widely understood. (Source: http://moneyterms.co.uk/ethical-prescription/)

- Vaccines
  (A substance with the potential to enforce immunity for some disease)

Furthermore pharmaceuticals can be divided according to the type of molecule comprising the active pharmaceutical ingredient. Typically these fall into one of these 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 of today are small molecular structures. Most biopharmaceuticals are ethical drugs because these drugs have a more recent history and so are still protected by patents. In this paper when referring to pharmaceuticals, vaccines and biopharmaceuticals are included.

Our definition of big pharma includes the top 50 pharmaceutical companies in terms of yearly revenues. The list being used has been compiled by Pharma Executive and is based on the sales of prescription drugs in 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 of the businesses have been omitted. The companies included in the study are listed below.

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

Figure 1: ***Pharma Executive Top 50 pharmaceutical companies***
Source: http://www.pharmexec.com/pharmexec/data/articlestandard//pharmexec/272006/354138/article.pdf

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

[10] Gray, 2006,
<http://www.pharmexec.com/pharmexec/data/articlestandard//pharmexec/272006/354138/article.pdf>

The companies included in this list are all fulfilling (or close to fulfilling) the only clear-cut definition of big pharma found in the literature[11]:

1. Sales of (at least) $2 billion a year
   This is accomplished by the 37 top companies on the list, with the entire list having yearly revenues above $1.2 billion.
2. International Operations
   Including the sales operations, 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 of the 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. Criteria 1 (yearly sales of $2 billion) should rather be seen as an indicator on the probability of fulfilling the other three criteria if no other information than sales are assessed. Furthermore, the advantage of a generous definition, including as many as 50 companies, makes it possible to explore different subsets of the data and also provide a larger sample to base the analysis on.

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 70's and 80's as spin-offs from biotech universities (mostly in the USA) and they produce only 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 make any distinction 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 term 'big pharma' or 'top 50 pharmaceutical companies' are both referring to the 50 companies listed above.

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

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 into a number of areas: drug development and manufacturing, medical devices, and medicinal, environmental, nutritional, and agricultural applications of biotechnology. The scope of this paper is on 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 to $640 billion (2006), with the largest markets being the USA 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 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]

A characteristic of the industry is the marked focus on R&D. For example, looking at the top ten companies in terms of total revenues, average R&D expenditures as percentage of revenues was 23.8% in 2005[14]. One aspect of this is the fact that the cost of drug development is getting higher as the drug is getting closer completion; this gives rise to a situation where only the large companies have the capital needed 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 seldom originating from a research group. In general, these companies are focused on research - and their manufacturing, sales and marketing capabilities are limited.

The second category is the medium size firms, making up some two to three hundred companies. The companies within this group have evolved further from the first group and have 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 what 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

[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.
[15] Laestadius, 2007, [Personal communication].

and continuing further 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 groups in the small and medium sized companies, which falls outside the scope. Big pharma are coming from the outside, whereas the smaller companies generally grow from within a region.

3.3 Process of drug development

Discovering and producing one new drug cost pharmaceutical companies about $900 million and on average it takes 8-12 years to develop a drug. New medicines are developed as follows[16]:

1. Discovery research: the development of a drug begins in a laboratory with chemists and scientists that search 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: in 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' effectiveness 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 Federal Drug Agency (FDA) in the USA or other regulatory agencies, to begin clinical testing on humans.
4. Clinical testing consists of phase I-IV. Phase I tests involve healthy volunteers to verify safety by studying how the drug is absorbed, distributed, metabolized, and excreted. Phase II involves volunteer patients (people with the disease) to determine effectiveness and further study the safety of the candidate drug. Phase III involves a larger group of patients in clinics and hospitals to test the effectiveness and the safety of the drug, usually in randomized and 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 FDA requires additional studies, namely phase IV. Phase IV studies expand the testing to a broader patient population and compare the long-term effects[17].

[16] *Pharmaceutical Industry Profile 2006*, 2006, <http://www.phrma.org/files/2006%20Industry%20Profile.pdf>
[17] Ibid.

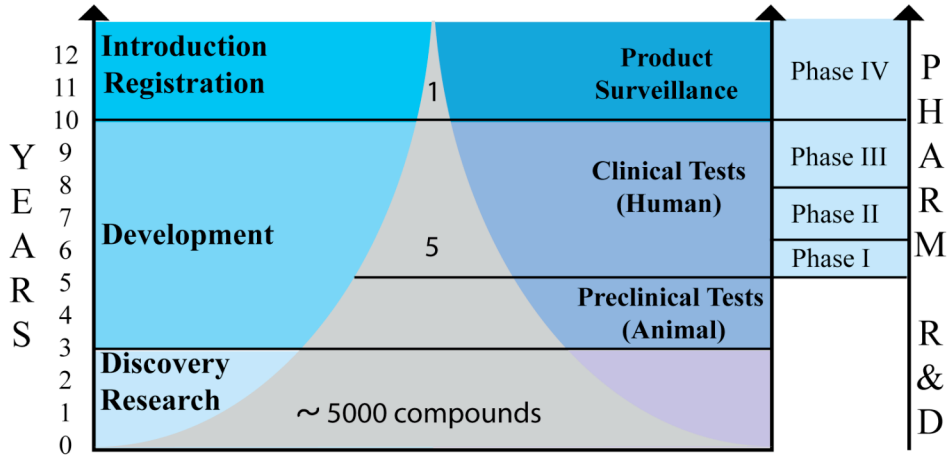

Figure 2: ***Drug development process***
(Source: http://www.phrma.org/files/2006%20Industry%20Profile.pdf)

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 the pharmaceutical branch was later moved into a subsidiary or an independent company. Looking at the companies included in this study, a correlation between the starting year and the rank on the revenue top list can be found. The older companies are generally placed higher on the list i.e. has 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 specialized in pharmaceuticals, and to a lesser extent active in other business areas. During the first half of the 20th century two major discoveries were made that had a huge impact on the industry, penicillin in the 1920's and insulin in the 1930's.[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 USA seized under the *trading with the enemy act*[19]. Examples of this are companies like Merck, formed from the US branch of Merck KGaA[20], and Schering-Plough[21], originating in the US branch of

[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." 6 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>

Schering AG (now Bayer-Schering pharma). Secondly, significant parts of production plants and laboratories were destroyed during the wars (especially during the World War II), mainly in Germany and Japan. Thirdly, the wars created a high demand for medical treatment and pharmaceuticals and thereby also creating greater incentives for finding new and more effective drugs.

3.4.3 Consolidation

The pharmaceutical industry is highly consolidated as an effect 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 generally are less prone to invest in drugs generating smaller revenues (typically below $100 million yearly). These drugs could then be bought by smaller more specialized 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 specialization on manufacturing. Such companies are growing quickly at present. An example of this is the aggressively growing generics manufacturer Teva and Sandoz, a division of Novartis. Countries such as China, with a weaker protection of intellectual property, have a thriving generics market.[24]

3.4.5 Rise of biotechnology

In the 1970's and 1980's the first major biopharmaceutical companies were founded by pioneers such as Amgen and Genentech. These companies often sprung out of individual research groups. During the 1980's a lot of them were forced to partner with major pharmaceutical companies to survive. A great many of the smaller companies have been acquired to add to 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 to be able to capitalize on such drugs, when the patents of some major biopharmaceuticals expire[26].

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[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>
[24] *Generic Pharmaceutical Association*, <http://www.gphaonline.org/>
[25] Piribo Ltd, 2005.; Vettel, , 2006.
[26] Sandström, 2007, [Personal communication].

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 focus on core competencies and outsourcing. It can also be seen that big pharma is lacking innovation momentum. Pipelines are weakened 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, e.g. pharmaceuticals specially designed for the specific genome of the individual. Whether big pharma will be able to survive in their current form, as fully integrated pharmaceutical companies, is a matter of debate and will be discussed further in the end of this paper.[29]

[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)

[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 logic connection between cause and effect. Using this approach knowledge of the world is based on empirical data and analysis of said data. The approach of the first part of this paper is descriptive and explorative, trying to give a view of localization of the studied companies.

Based on the results of the initial empirical study, and original research questions, further research questions were identified. 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 localization as proposed in this study is the longevity of the investment and the commitment to both the investment and the region. Therefore, 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-intensive.

Furthermore, the study was limited to only include operations involved in research, development and manufacturing of human prescription pharmaceuticals, excluding 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. The most obvious parameter in a study on localizations, the geographical location, was in this case represented by a city and a country. This parameter is necessary in order to do a geographical study, however it can be argued that it should have been divided into other entities, rather than countries or cities. However, in a study such as this, working with close to 1400 units on a global level, inclusion of new entities would complicate the data collection and cause too much additional labour.

To be able to unravel the dynamics of the localization 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. To the largest extent 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. The same goes for a sold (closed) unit, where the selling year is stated as a closing year. When a unit is sold between two companies included in the study, a peculiar effect is seen; a unit transferred between two companies in the study will show as one new unit and one closed units.

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 localization. This information was hard to find, and is 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. Also comments were added, most often referring to acquisitions of units or irregularities in the information. A screenshot of an example page of the excel database can be seen below, it is sorted by company, the example is from the database sheet of Amgen.

	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

Figure 3: ***Database screenshot***

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

[30] Form 10-K is a report to the US Securities and Exchange commission yearly, giving an overview of the business activities and financial status of the enterprise.

releases. The second category, the 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 has the purpose to promote the own company. Therefore, it is not objective, although the information about most aspects of localizations seems to be accurate, for example when comparing to studies such as *Big pharma in Europe* by Björkman[31].

One aspect of the localizations has provided more difficulties than the other when it comes to using corporate information, namely the closing of plants. During the study it has been observed that the companies are reluctant to publish information that can be interpreted as negative, such as closure of factories. However this information can to a larger extent be assessed using other more objective sources, for example newspapers.

To assess the quality of data an evaluation was carried out based on the companies' own published number of their total number of R&D and manufacturing units. By comparing this with the data collected in the empirical study a measure of *coverage* of our data was established. However, this is not to be seen as a definitive number, but rather 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 total number of 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 with 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 of 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 the size, for example in terms of investment or staff. Making a geographical mapping to a larger extent based on the size of the units is an area for further research and it 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 and furthermore only a very limited number of persons have an overall view of the localization of these companies. For this paper the gathering of information for the empirical study from the sources mentioned earlier was deemed most fitting.

[31] Björkman, 2007, [Personal Communication].

Presentation

This section contains the presentation of the empirical data collected for this study. The data will be presented by figures, text and diagrams to give an overview of the localization of big pharma. The presentation will not contain all of the data collected, but rather give an overview.

5 Empirical Data

This chapter provides an overview of the results of our empirical study of big pharma localizations. 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. All data in this chapter is gathered from the database containing the results of the empirical study, unless otherwise stated.

Sorting the units by country is a bit problematic and does not necessarily give a correct view of the localization, due to regional difference within the country. For example the units in the USA are generally located in the states along the east or west coast or in the Chicago area. However, to give an overview of the big pharma presence this way of visualising the localizations were chosen anyway. One reason for this is the difficulties to separate the units by regions in a stringent manner. However, maps showing clusters or agglomerations have been created to give a more exact view of the worldwide distribution of units. These maps of agglomerations are showing the units gathered as clusters, sorted after geographical proximity. Units included in a cluster on the map lie within a circle with a radius of 50 kilometres.

5.1 The geography of big pharma R&D

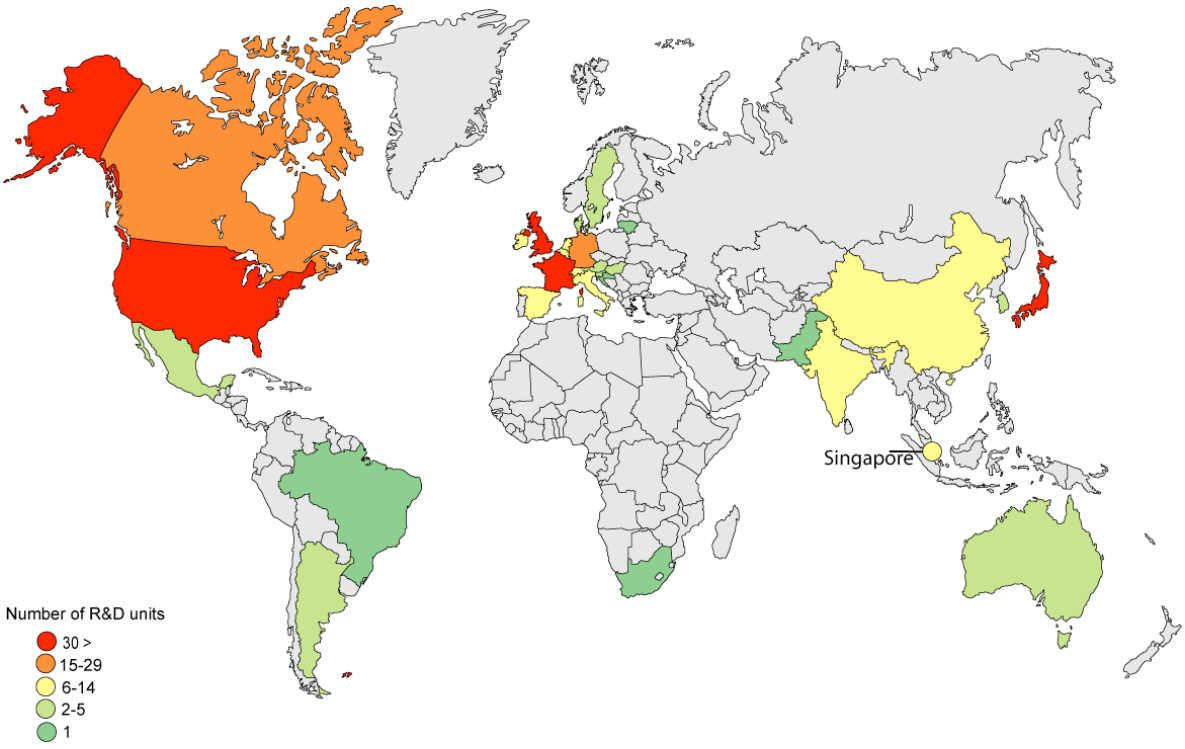

Figure 4: ***Concentration of R&D Units***

As can be seen in figure 4, 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 huge differences in terms of number of units. For example the USA has nearly five times as many R&D units as France. The numbers are shown in greater detail in figure 5, where it can be seen that the USA has by far the most R&D units (147), followed by Japan (63), United Kingdom (39), France (30), and Germany (22).

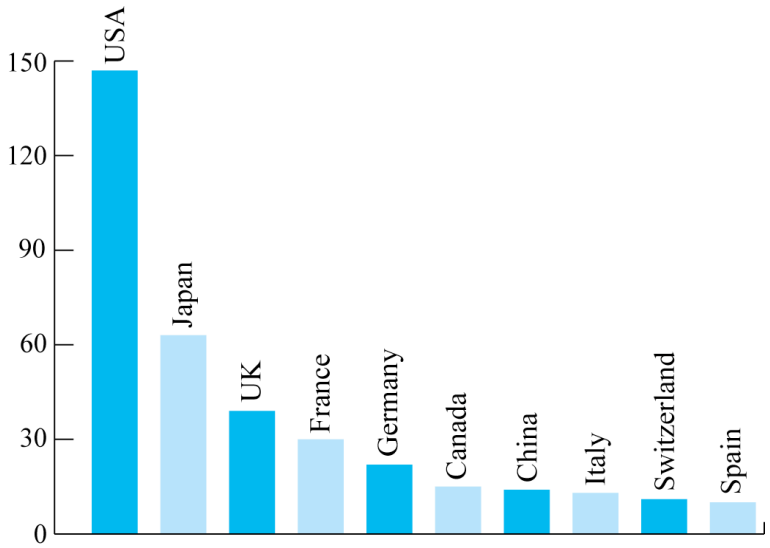

Figure 5: ***Top countries ranked by number of R&D Units***

5.1.1 R&D agglomerations

The cluster map in figure 6 has been created out of the data collected of localizations 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 USA, in Western and Central Europe and in Japan. Important areas here include the Boston/Cambridge area (Massachusetts), the Californian cities San Diego, San Francisco and to some extent Los Angeles, Paris and Osaka.

To be noted is that in the following map, with enlargement of certain areas, no clusters are hidden behind the enlargement. The same is also valid for the cluster map of manufacturing units.

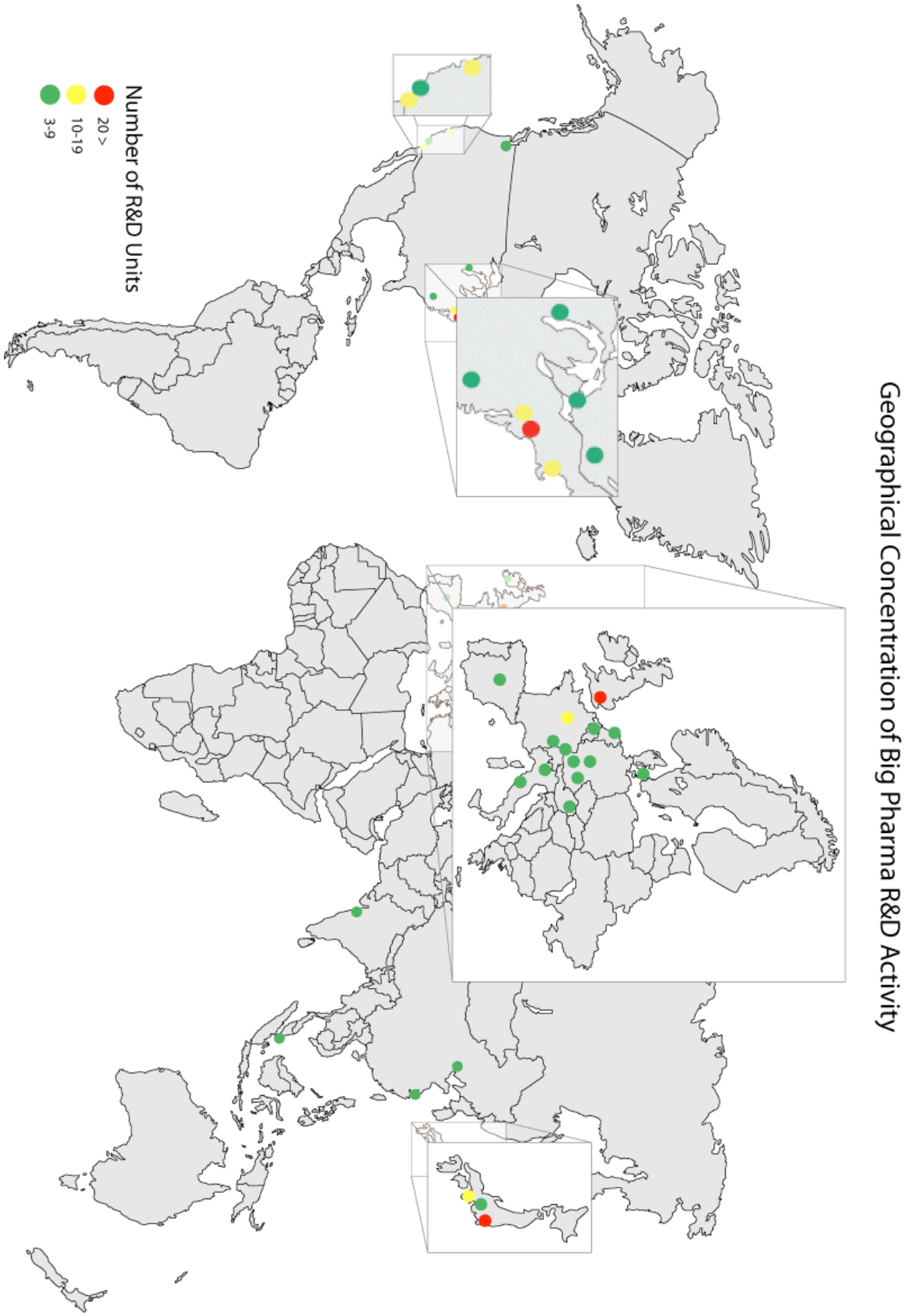

Figure 6: ***Concentration of R&D Units shown as clusters***

5.2 The geography of big pharma manufacturing

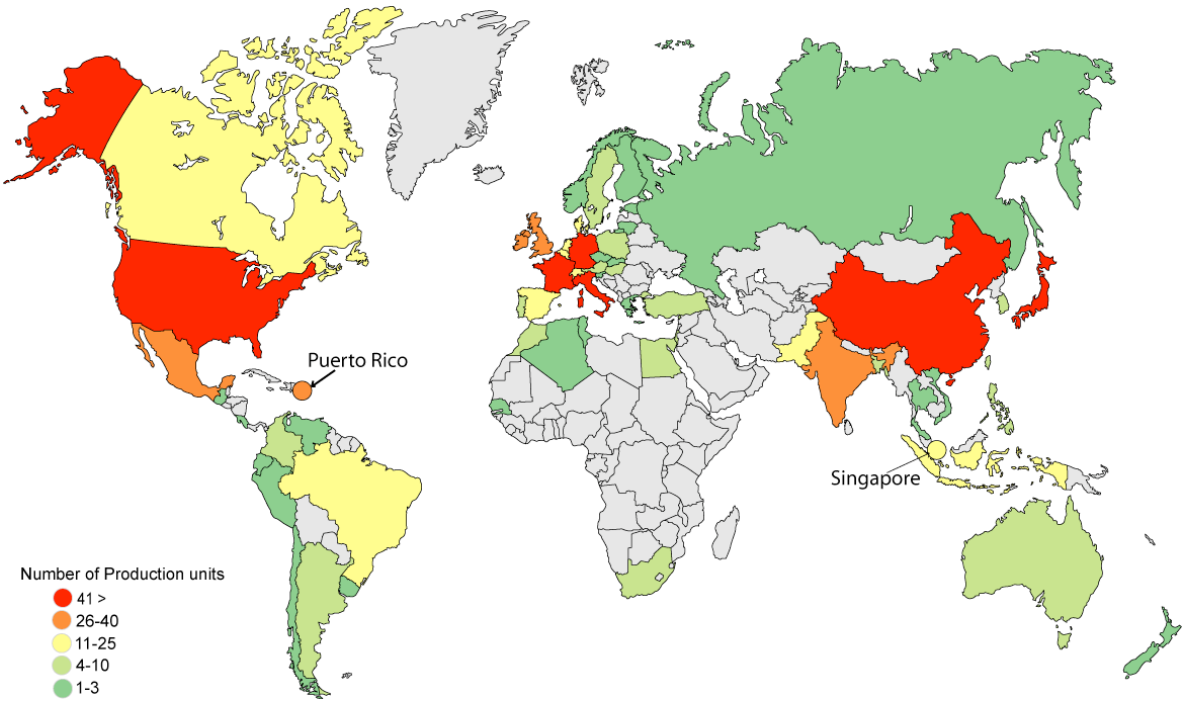

Figure 7: ***Concentration of Manufacturing Units***

As for the R&D operations, the manufacturing units are mostly situated in North America, Western Europe and 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.

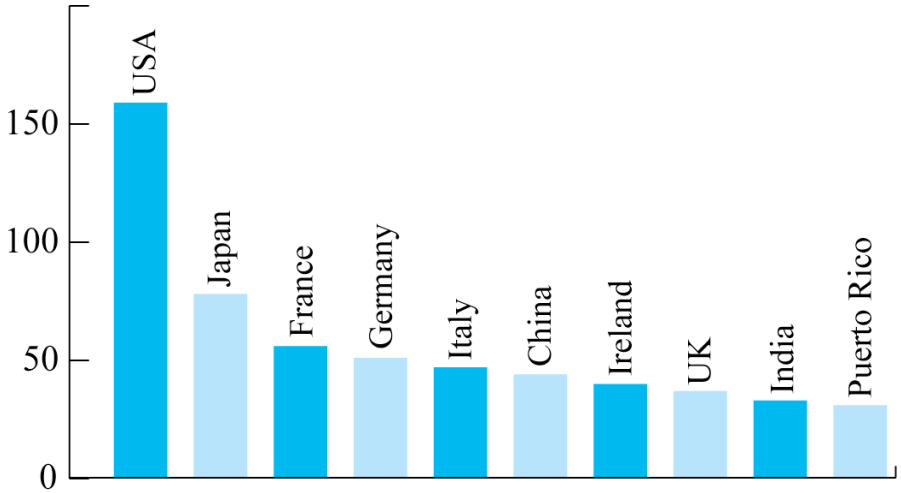

Figure 8: ***Top countries ranked by number of Manufacturing Units***

The diagram in figure 8 shows the distribution of manufacturing units among the top countries, similar to the R&D units USA (159) is in the top, followed by Japan (78), France (56), Germany (51), and Italy (47).

5.2.1 Manufacturing agglomerations

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

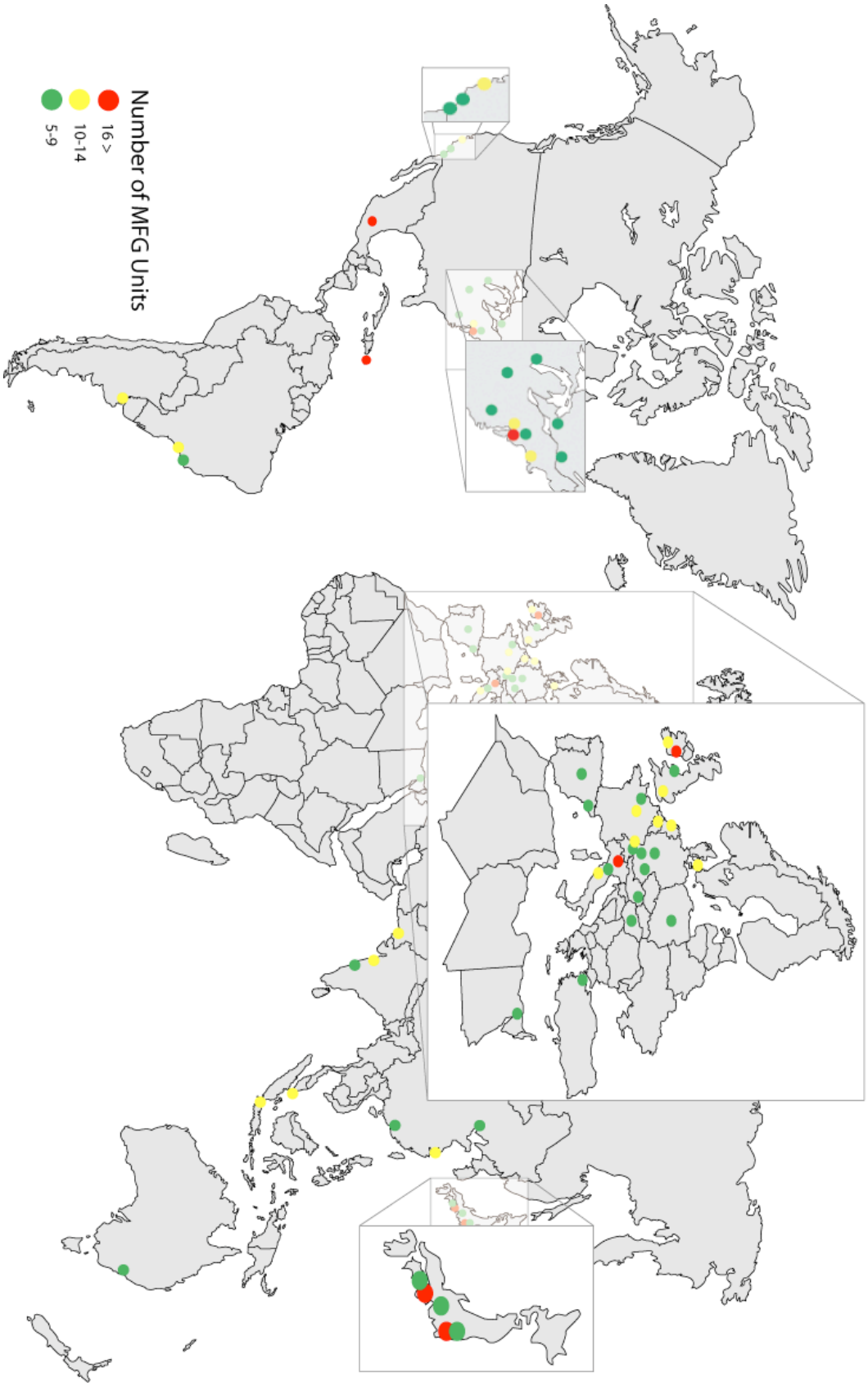

Figure 9: ***Concentration of Manufacturing Units shown as clusters***

5.3 Regional comparison

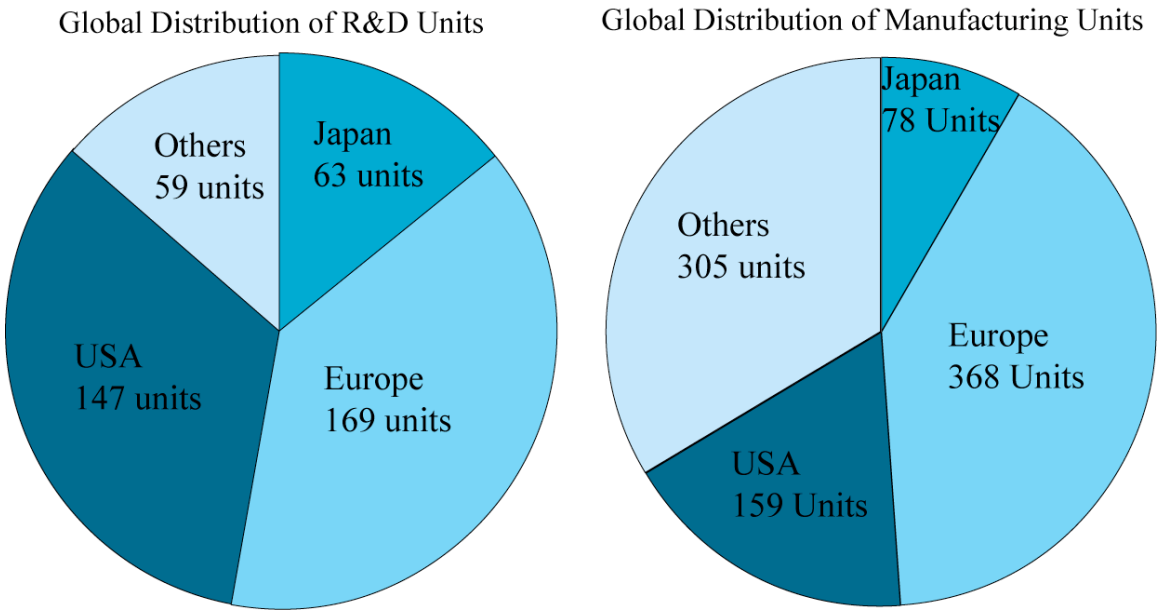

Figure 10: ***Comparison of the USA, Europe and Japan***

Figure 10 is 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 USA, the European Union, including Switzerland, and Japan, representing 45%, 30% and 9% respectively of the world pharmaceutical market in 2006[32]. This comparison shows quite an even distribution between the USA and Europe in terms of R&D units, whereas for manufacturing units Europe has almost twice the number of the USA. Japan has around half the number of units compared to the USA, in both categories. In manufacturing the largest parts of the other slice, are units located in China, India and Puerto Rico.

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 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 no announced 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

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

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 46 billions SEK out of a total 59.3 billion SEK (2006)[33]. The dependence on a single company is a risk. AstraZeneca has announced their 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.

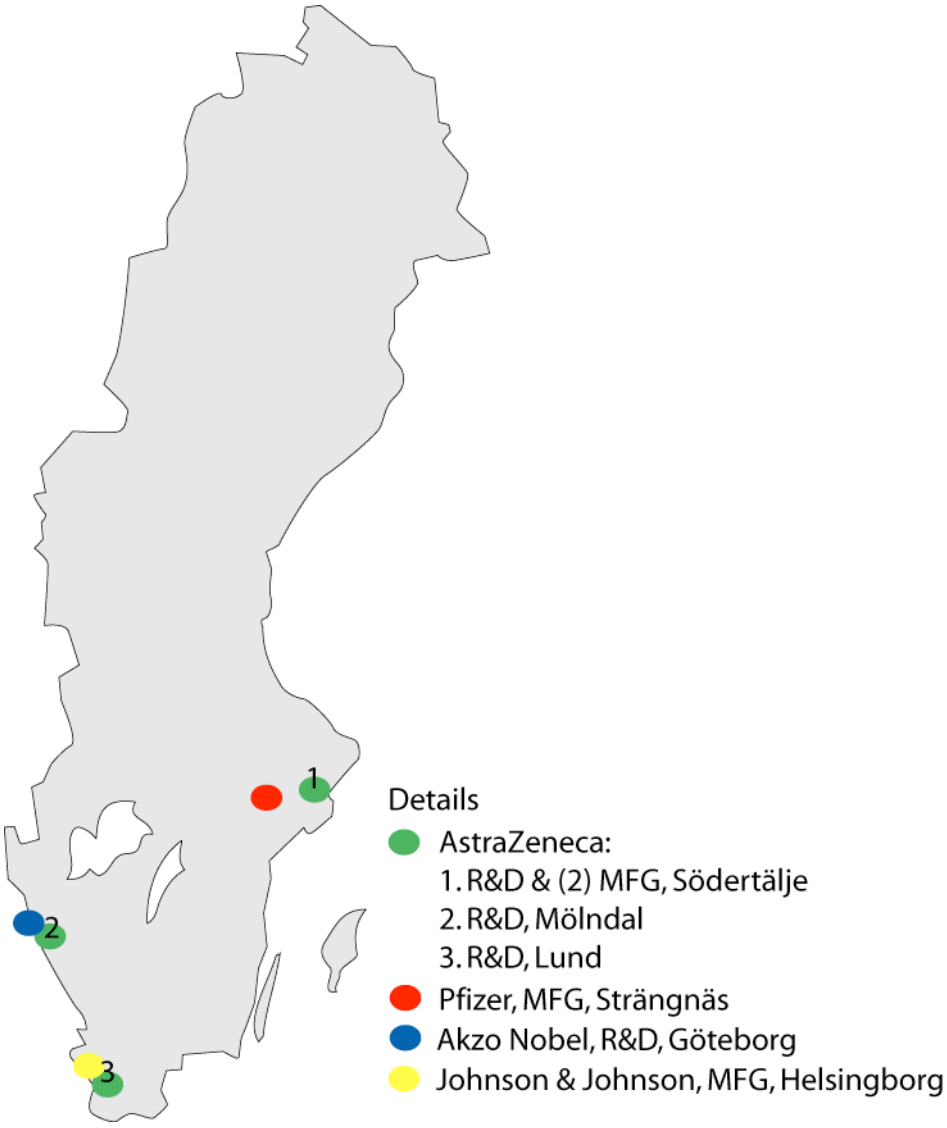

Figure 11: **The big pharma geography of Sweden**

[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>

6 Trends in Big Pharma Localization[λ]

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

6.1 Global

The changes in geographical localization 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 has been compared over the last 10 years, e.g. from 1998 to 2007 also including the plants that are under construction, planned to be constructed and planned to be closed.

The closing of plants has been investigated as a part of the larger study. The data indicates that most plants are closed down in the USA followed by Japan, France, Puerto Rico, 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 that there is no significant trend but rather a closing of a certain percentage of the active plants. In line with this, USA, the country with the largest big pharma presence, shows the most closing of old plants and founding of new plants. However, at least two significant divergences from this general rule can be spotted – the trends of close downs in Puerto Rico and Japan.

In Puerto Rico close to 30% of the plants active ten years ago have been closed down. Puerto Rico saw the beginning of its rise in the pharmaceutical industry some 40 years ago, and has since then been the home of a great many pharmaceutical manufacturing units for most of the major companies. Consequently, the last ten years have shown a major switch. When the major companies established themselves in Puerto Rico, the most important reasons were economical, such as tax incentives and other incentives given to foreign companies. However, this seems to be changing now; the old tax laws are expiring the coming year and the decision-makers currently seem to have a hard time agreeing on a new set of laws[34]. This is making investors nervous, and might be a reason behind the closing of plants in Puerto Rico. Furthermore, the cost of electricity is rising, decreasing the economic advantages of Puerto Rico. Other reasons stated by the companies in press releases are more general, and include excess capacity, expiration of patents and quality control issues. It can be noted 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 an increased degree of consolidation in the Japanese pharmaceutical industry, where capacity has been optimized and slack removed as a result of mergers and acquisition, creating a need to close down excess units.

In the opening of new plants some interesting trends can be found, the most important one is a shift in the new localization of the industry towards Asia. Similar to the closing of

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

plants, the USA 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 to a significant extent R&D as well. The empirical study has shown that around 25% of the total units in China and India, and 35% 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. For example 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 operations, than in R&D operations. A reason for this focus on outsourcing is that manufacturing is not the core competencies of these companies. If this is the case, no competitive advantage is to be gained from it and it should be outsourced, according to Prahalad and Hamel[37]. This view has been confirmed in two interviews with managers at AstraZeneca experienced from the manufacturing organization. They state that "there are no competitive advantages to be gained from manufacturing for AstraZeneca" [38]. Although this may be a bit rash it still bear witness of a view in the industry that the focus should be on research and commercialization, whereas manufacturing is a necessity, but of less strategic importance.

Also the buying of smaller companies to acquire a patent or to fill pipelines could be seen as an example of increased focus on R&D. 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, have recently created subsidiaries to which all manufacturing has been transferred. This is also in line with the focus on the core competence.

6.3 Consolidation

Although the industry is dominated by a few major players, there are a vast amount of other companies on the market. This can be illustrated by the relative market shares of the

[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.
[38] Haeffler, (Project Director, AstraZeneca), [Interview], 2007.;
Johansson, (Vice President of Supply and Capability, AstraZeneca), [Interview], 2007.

companies: The top ten companies were responsible for over 40% of the total industry sales 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 in figure 12.

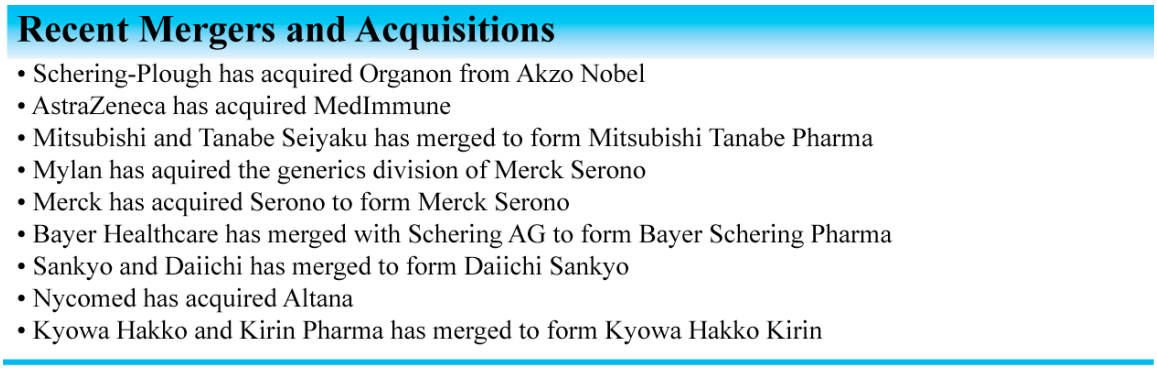

Figure 12: ***Recent mergers and acquisitions***

The mergers and acquisitions in the pharmaceutical industry are usually driven by one of two main purposes. Either the companies are trying to stream-line their operations or to acquire the pipeline of another company. The first category of mergers and acquisitions are usually more comparable in size. Examples of this is the merger of Bayer Healthcare and Schering AG. The second category is usually a bigger company acquiring a small company, that usually focus purely on research but lacking the capabilities to commercialize the research. As the pharmaceutical is moving through the drug development process and gets closer to being a finished drug the higher the costs get, i.e. 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 a growing competition from generics companies. The generics companies are able to sell drugs cheaper, mostly due to much lower research and development costs than the traditional pharmaceutical companies that sometimes are spending over 20% of their revenues on R&D. The generics sector is undergoing a globalization; the prime example of this is 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 quickly growing pharmaceutical industries of China and India. However, except for TEVA, these generics companies have too low revenues to be included in this study.

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

Analysis

This section will first present some localization 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

In this chapter some general concepts and theories regarding location of manufacturing and R&D operations are presented. 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[41], drawing on research by Machlup[42], identifies three general types of views on localisation following three different perspectives of the firm; the neoclassical, the behavioural and the institutional.[43]

The neoclassical view sees location as a means to minimize cost and maximize profits. The firms act as *economic persons* adapting to the laws of supply and demand 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 firms are considered to possess some amount of power, the location decision is seen as a bargain between different regions and the firm.[44]

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[45].

[41] Hayter, 1997.
[42] Machlup, 1967, pp. 1-33.
[43] Hayter, , 1997, p. 80.
[44] Ibid.
[45] Nishioka & Krumme, 1973, pp. 195-205.

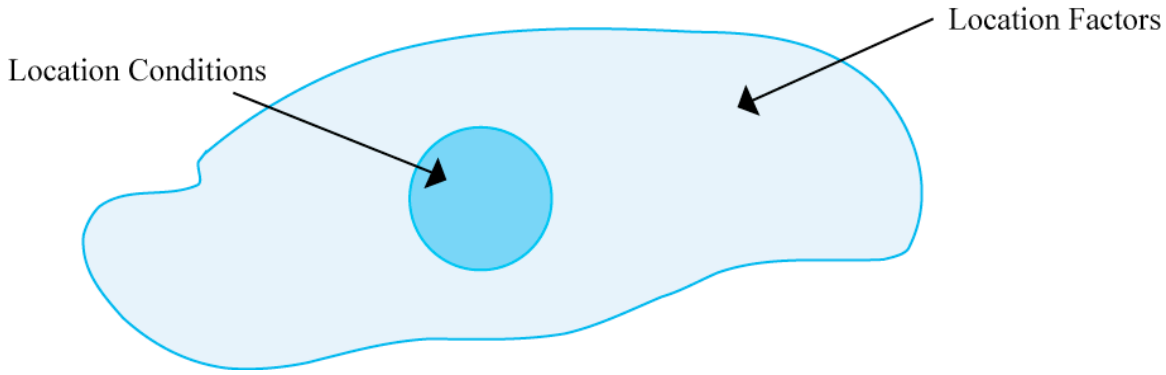

Figure 13: ***Difference between location conditions and location factors***
(Source: R Hayter, The Dynamics of Industrial Location)

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[46].

In this report the theoretical standpoint will be most similar to the institutional theory. That is, the geography of big pharma is regarded as the result of a process influenced by different actors. Naturally big pharma themselves are central actors but so are governments and regional organizations 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[47], be described using five forces of competition. 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.

[46] Hayter, 1997.
[47] Porter, 1990.

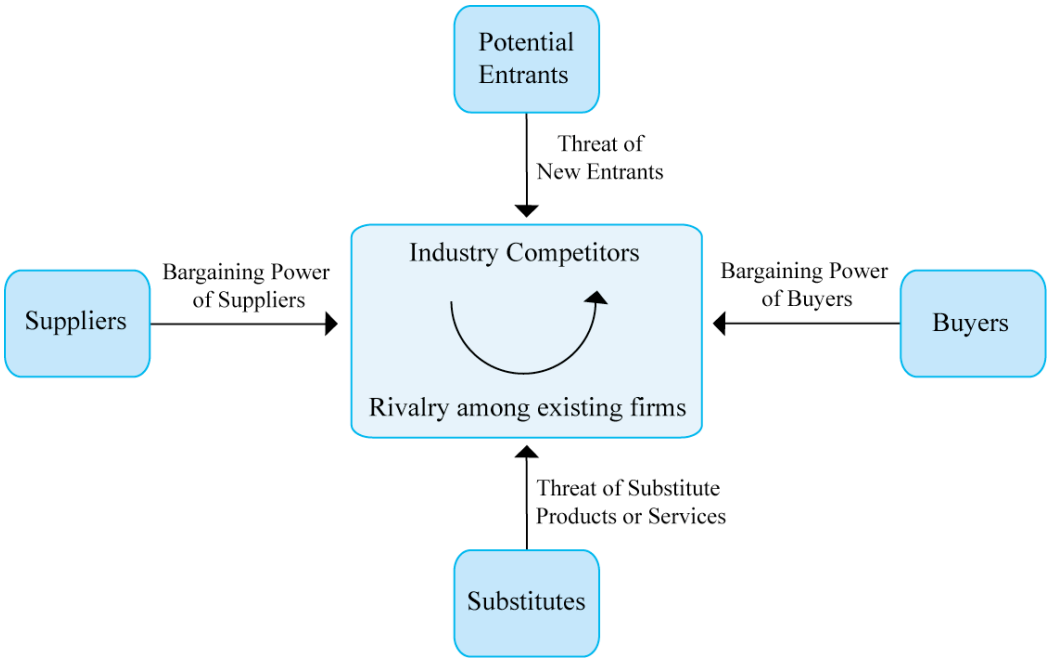

Figure 14: ***Porter's Five Forces***
(Source: M E Porter, The Competitive advantage of nations)

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 organization 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 figure 15. These factors explain why some nations are successful in a certain industry, and why some nations terribly fail. This section will summarize Porter's theory on the determinants of national advantage. [48]

[48] Porter, 1990.

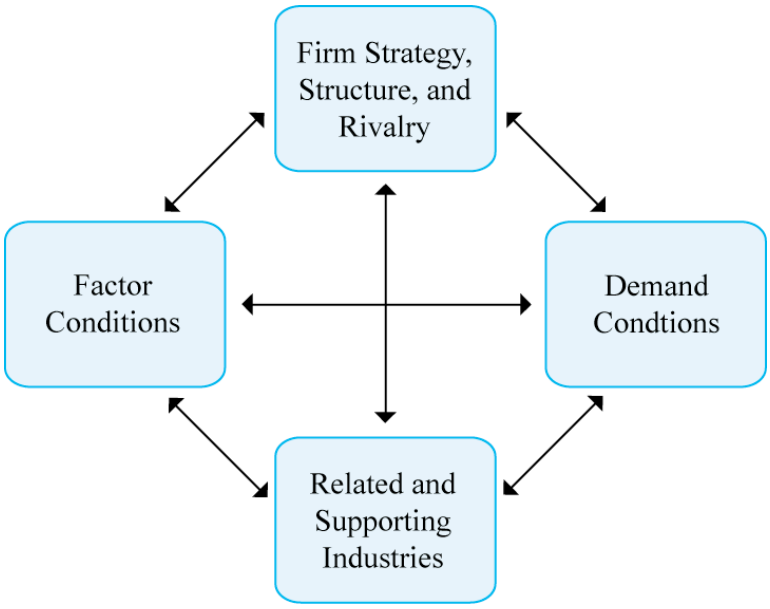

Figure 15: ***Determinants of national advantage***
(Source: M E Porter, The Competitive advantage of nations)

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 generalized 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, organized 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 maintain several drug discovery research centres. A large number of those are located in geographic *clusters* of pharmaceutical research activity. The knowledge generated by research, especially the basic scientific knowledge, runs more rapidly and broadly to geographically nearby areas than to distant locations[49]. 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[50]. 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 tend 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 reduced search costs and generation of competitive pressure to innovate[51]. 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 dollar, access to capital is therefore critical. The industry is dependent on federal government research funding and venture capital, localization in such regions is therefore favourable[52]. The stability of the environment is critical for the localization 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 USA that airport accessibility and direct flights is a high priority in the location decision.[53] Closeness to airports encourages services to clients, researchers from abroad and minimizes 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*

[49] Jaffe, Trajtenberg, & Henderson, 1993.
[50] Zucker, & Darby, 1997.
[51] Porter, 2004, pp. 65-67.
[52] Dibner, 2001.
[53] Echeverri-Carroll, 1999.

geographic proximity that gain performance advantages through co-location".[54] 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 symbolize a combination of competition and cooperation. Strong competition occurs in winning customers and keeping hold of them[55].

7.4.3 Cluster growth and development

What drives the industry cluster development and growth is a common subject discussed in the 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 specialized supplier networks to serve the larger companies in the cluster[56]. Even though cluster policy is

[54] Doeringer & Terkla, 1995, pp. 225-237.
[55] Porter, 1990.
[56] Doeringer & Terkla, 1995, pp. 225-237.

important, there are some general criticisms of cluster policies, Rosenfeld present some points[57]:

- 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, specialized 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 internationalization[λ]

As a description of R&D in the pharmaceutical industry, especially in the largest companies, Gassman and von Zedtwitz' model of R&D internationalization can be used. According to this model research (R) and development (D) can be organized in one out of four ways. The research units can be geographically centred (domestic) or geographically scattered (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 organization.[58]

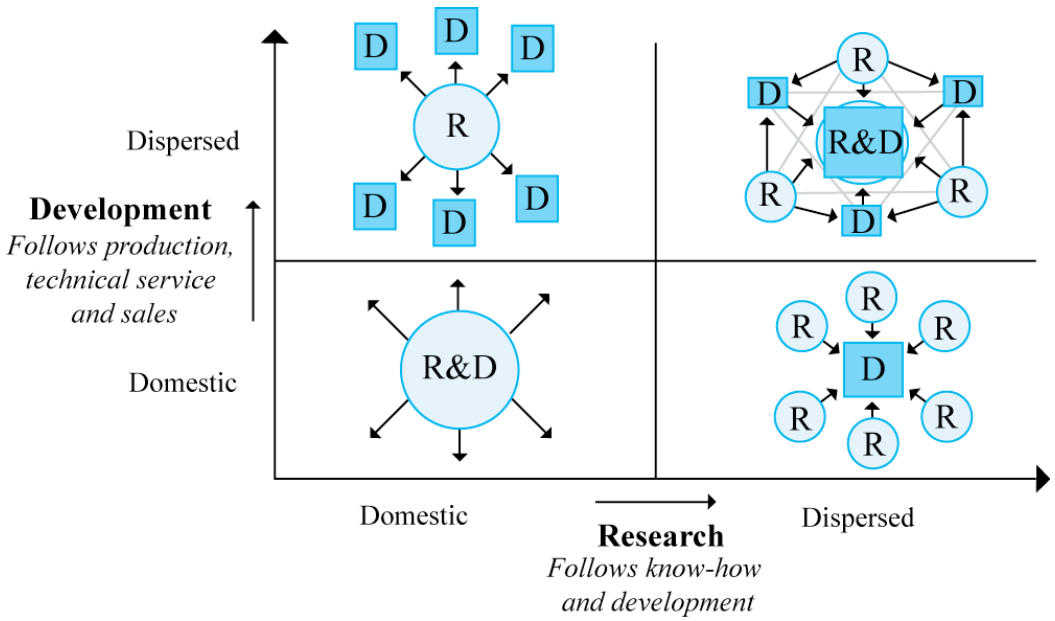

Figure 16: ***Model of R&D Internationalization***

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

As an explanation for these four types of organization, Gassman and von Zedtwitz describes two main drivers, localization of research units is driven by technology and localization 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

[57] Rosenfeld, 1995.
[58] von Zedtwitz & Gassman, 2002, pp. 569–588.

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.[59]

[59] von Zedtwitz, & Gassman, , 1998.

8 Localization in the Pharmaceutical Industry[λ]

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

8.1 R&D localization 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 internationalized companies both in manufacturing, research and development, thus the general view of these companies is that of a global R&D organization. As for smaller companies the research is increasingly domestic or geographically centralized, a market driven R&D organization. For even smaller companies the development as well is centralized, a national treasure R&D organization. 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 organization (both research and development are internationally dispersed) or market driven R&D organization (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 organization geographically dispersed, creating a global organization.

According to literature an exception to the global R&D organization is the Japanese pharmaceutical companies which to a higher degree than the European or American companies rely on a domestic research and development organization. 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 localization 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 localization 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 organizational 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 localization 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.[60]

8.2 Localization of manufacturing

Compared to R&D the localization 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 centralized 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 generalized set of drivers may be hard to establish, however a number of criteria can be identified.

Possibly the most important parameter in localization decisions is the tax system combined with the judicial system.[61] 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 economical incentives to companies that are establishing operations in the region, such as lower taxes.

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 localization 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

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

in the global economy of today, thus giving rise to a need for access to international airports.[62]

Also factors affecting the quality of life for the staff are important. This could include quality of schools, the 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. [63]

8.3 Localization of biotech operations

Localization of biotechnological production has in large the same drivers as the rest of the production, however it is to a higher degree 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 working at one location does not necessarily work and give the same result at another place.

The new localizations of biotechnological production are scattered, but it is found that most of them are in the USA. Furthermore, Canada and Singapore are also important locations for new biotechnological factories. Noted from the study is that this particular type of production seems to a lesser extent to be located in low cost countries, probably because of the higher technological demands forcing a dependence on a higher skilled workforce.

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

9 The Ideal Company[λ]

To analyse the reasoning about localization and to determine the degree to which localizations are governed by rational and logic consideration a comparison between the real world and an *ideal* case will be presented in this section. The comparison has been 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[64] (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.*[65]

The executives represent 13 companies from the top 35 pharmaceutical companies based on revenues, including eight of the top ten companies, and one company that is 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 localization of a pharmaceutical company.

The results of the above mentioned study shows a picture of the "ideal" company with clear similarities to the recent trends in the industry. The answers of the executives are shown in figure 17. What may be most surprising is the manufacturing unit located in Portugal, a country with a quite limited presence of big pharma, 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 corporate tax in Portugal compared to many other Western European countries.

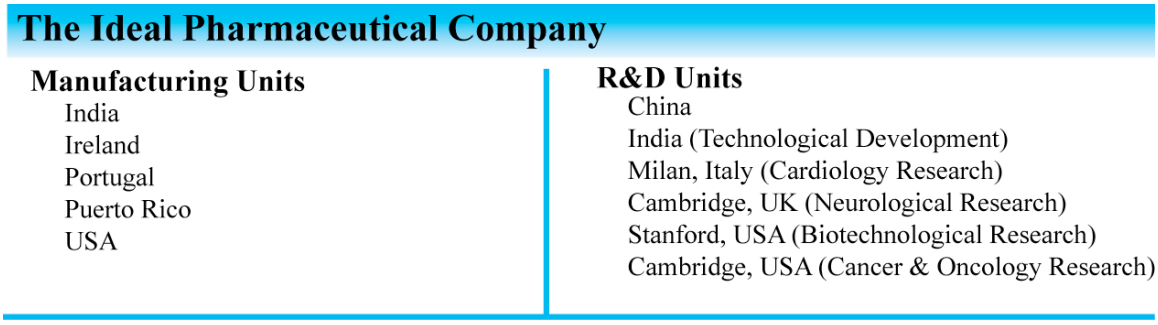

Figure 17: ***The ideal pharmaceutical company***
(Source: NERA Economic Consulting, Key Factors in Attracting Internationally Mobile Investments by the Research-Based pharmaceutical Industry)

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

Based on these answers provided in the report from NERA Economic Consulting a comparison with the empirical data collected in this study was made. This comparison could show indications about the rationality in location decision, for example give a hint about the role of history in new establishments. First of all according to the empirical study conducted the "real" pharmaceutical company with five manufacturing units and six R&D units would be distributed as shown in the following figures. Figure 18 shows the distribution based on the entire study, while figure 19 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 differing between the *ideal* and the *real* company.

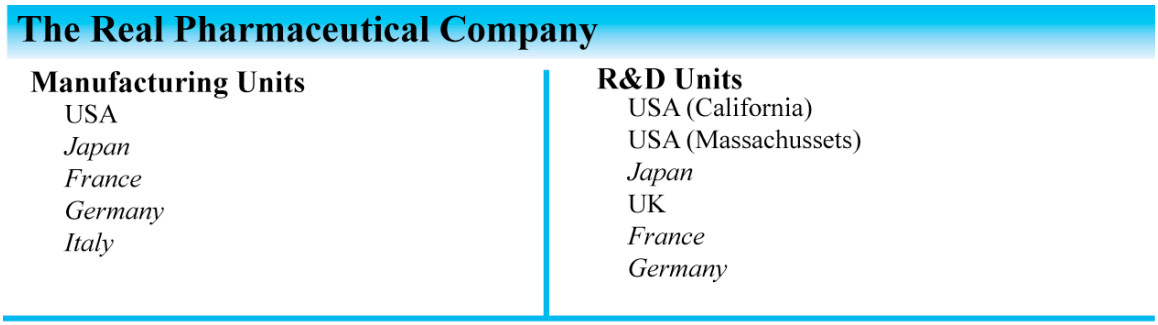

Figure 18: ***The real pharmaceutical company***

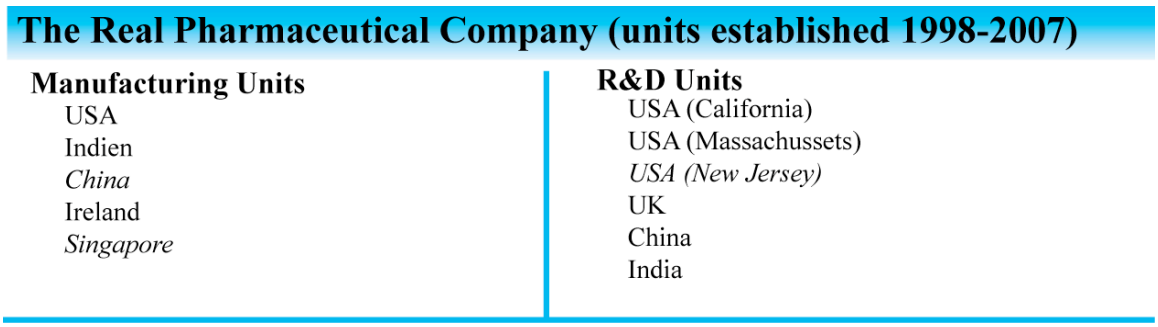

Figure 19: ***The real pharmaceutical company 1998-2007***

As seen by 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. This is logical since these localization decisions should follow the view of the executives, and should be part of the same paradigm in pharmaceutical localization. However, regarding all of 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 globalized 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 investments bind the company to the region. Furthermore, previous investments in a region may also have created an increased competence, thus making the region more attractive for future investment in relating fields, both for the own company and for others.

In conclusion, the recent establishments of new units converge 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, however more interesting is the divergence between the older localizations and the idea of the ideal company. The impact of history may be one reason for this; another reason may be the changes that have occurred in the industry and in the world economy altering the drivers and regional conditions governing localization. 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 localized in proximity to previous units within the company.

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

Big pharma are 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*.[66] 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.*[67]

No doubt big pharma are Trans-national Corporations (TNCs) in the sense that they have "the power to coordinate and control operations in more than one country"[68]. Thus, explaining the geography of big pharma R&D would most likely be linked to the *strategies of TNCs*. However, these strategies are, especially within the R&D intensive pharmaceutical industry, 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.[69]

The character of technological change has a strong influence on the location of big pharma R&D units because TNCs are highly dependent on innovation[70]. In the end it is through such innovations – the discovery of new drugs – big pharma makes profits.

Moreover every location should be understood in 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. In figure 20 these relationships have been summarized.

[66] Dicken, 2003.
[67] Ibid., pp. 4, authors' italics converted to underlines.
[68] Ibid., pp. 198.
[69] Dicken, 1992, pp. 303-316.
[70] Dicken, 2003.

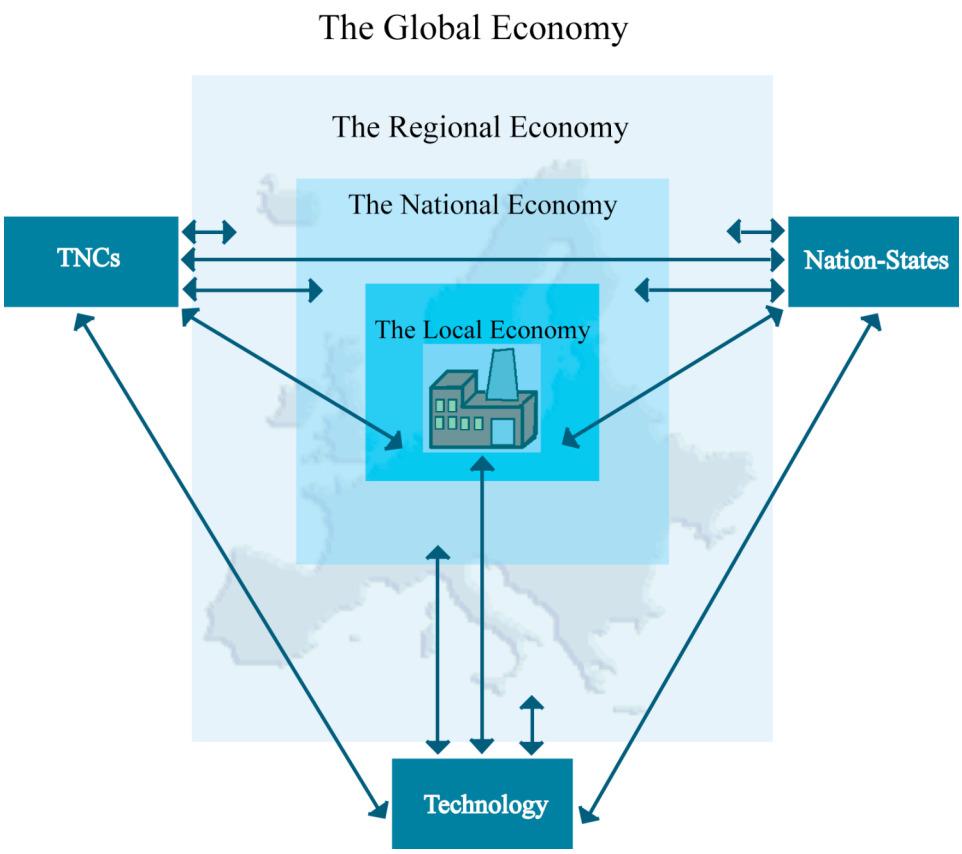

Figure 20: ***The Global Economy***
(Source: P Dicken, *Global Shift: Reshaping The Global Economic Map in The 21st Century)*

10.1 Purpose

In this chapter the intention is to outline some aspects of the theory presented in Peter Dicken's *Global Shift*[71] 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?

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 the 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 in this chapter is on the big pharma R&D units within the *European region* (EU-27[72] + Switzerland). Thus the study is limited to the 169 R&D units

[71] Dicken, 2003.
[72] EU-27: Austria, Belgium, Bulgaria, Cyprus, 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.

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, genetical engineering, peptide chemistry and cell biology are at the core of what may be called the *molecular biology revolution*[73]. This revolution should not be seen as an historical event with a fixed beginning and end. Some authors[74] claim the revolution started with the famous discovery of the double-helix structure of DNA by Watson and Crick in 1953 whereas some[75] 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 70's,

10.3 Method

The outline of this chapter consists of a presentation of some of the aspects of the theory as it is outlined by Dicken in *Global Shift*[76]. 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 isolation of the rest of the world. However, the ambition in this chapter is to keep the discussion about the theoretical entities separated and to relate this to the European region.

The focus in this chapter will then turn to 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. After that results will 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[77] 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*".[78]

[73] Henderson, Orsenigo & Pisano, 1999.
[74] Ibid.
[75] ABC Online, <http://www.abc.net.au/science/features/biotech/1970.htm>
[76] Dicken, 2003.
[77] Ibid.

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 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.* [79]

The exact configuration of R&D units depends to a large part on the organizational structure of the TNC as a whole. If a hierarchical style is used the firm is more likely to organize their R&D according to such fashion. On the other hand, if the TNC has less such influences the organization of R&D will be less centralised and more geographically dispersed.

In turn the organizational structure depends 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

[78] Ibid., pp. 198
[79] Ibid., pp. 243. Authors italics converted to underlines.

the information is person-embodied.[80] The reasons for maintaining international R&D activities are connected to the fact that key know-how is internationally dispersed.[81]

10.4.2 The strategies of national governments

Nation-states consist of a geographical containment in which a population with common cultural traits is organized by a common authority structure. Thus nation-states are containers of different types of resources and they have the ability to regulate activities within its boundaries. In that sense, nation-states are both *containers* of economic activities and *actors*. [82]

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

- *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 import of products and services into the country. *Tariffs* are taxes put on imports as a mean to reduce its competitive advantage in comparison to domestic goods. *Non-tariffs* are restrictions on imports of a diverse nature; they can be technical (licenses 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*.[83]

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 summarizes these policies in four broad categories:

[80] Patel, , 1995, pp. 141-153.
[81] Hotz-Hart, 2000.
[82] Dicken, 2003, pp. 123
[83] Ibid., pp. 132

- *Entry*. Governments may decide to regulate the establishment of foreign firms by different measures. It can for example uphold laws as to 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. In such a way 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 as to gain access to some of the profits made within national borders. Conversely, international enterprises wish to minimize such taxes as to maximise their own profits.
- *Stimulate*. Due to the increasing global dimensions of the economy governments may try to attract foreign investment in the competition with other nations. This can be done by introducing incentives and bid in a international, regional or national bargain process.

10.4.2.3 Industry policies

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

These include[84]:

- 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

[84] Ibid., pp. 139

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.[85]

Innovation, the creation of technology, 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 to be found in books or software. Such knowledge can travel over large distances by means of internet or other transportation or communication systems. Tacit knowledge on the other hand is difficult, not to say 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'*[86]

Evidence suggests that the national context can have a considerable impact on how such milieus are composed[87]. 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.*
- *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.*[88]

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 conscious creations of governments or other policy makers[89].

[85] Ibid., pp. 85
[86] Ibid., pp. 116
[87] For reviews of national innovation systems see for example Lundvall & Maskell (2000)
[88] Dicken, 2003, pp. 116-117. Authors italics converted to underlines.
[89] Ibid., pp. 117

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 in the following way:

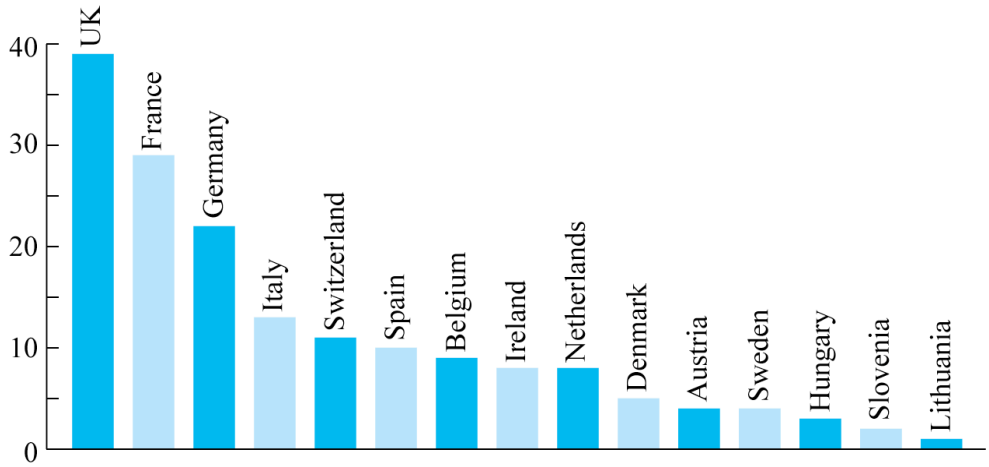

Figure 21: ***Number of big pharma R&D units in Europe by country***

It should be stressed that the data only contain the *number* of R&D units within each country. There is no appreciation of the size of these units in terms of money *value* or *workforce*. Thus one should be cautious in drawing too 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). Needless to say, location decisions taken in the 19th century were influenced by different factors than they are today. Thus to understand the snapshot of big pharma R&D units visible today we need to understand the historical context of the pharmaceutical industry.

10.5.1 The strategies of big pharma

Big pharma are *global-market* firms in the sense that their products 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 the big pharma R&D units tend to be located near acclaimed universities etc. This may to some extent explain the large amount of R&D units within the UK for example. In fact fair shares of these units are located near Cambridge University and London University.

Dicken stipulates that the dispersal of R&D units is coupled to the organizational form of the specific company. Disappointingly there is no uniform organizational structure typical for the big pharma chosen in our study. The reason for this is obvious; the companies were not selected on such ground and thus they are very different in the factors that, according to Dicken, influence the particular organizational 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. The companies in our study retain, on average, 40% of the R&D units within the host country. These low numbers in comparison to other TNC studies[90] suggest that big pharma locate 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 maintain R&D operations in Japan, America and Europe. On the contrary, most big pharma also have strong research centres in their host country. 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), UK (3), Belgium (2), Denmark (2), France (1) and the Netherlands (1). The European companies only retain about 20% of R&D units within the country of headquarter. Thus there is an even lower correlation between the number of big pharma with headquarter 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 USA and Japan and that many European big pharma are 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 national governments role 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 a relatively high numbers of big pharma R&D units in relation to their population and GNP.

It is well known that Ireland, perhaps more so than any other European country, ever since *opening* the economy in the 50's, aggressively have adopted policies as to attract investments. 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.[91] 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 since the turn of the century.

Switzerland has a profound history within the pharmaceutical industry. Chemical processing companies and dye manufacturers such as Ciba and Sandoz were among the

[90] Patel, 1995, pp. 141-153.
[91] O'Donnel, 1998, <http://aei.pitt.edu/27/>

pioneers in 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. Especially the Swiss enterprises are known for their smooth business transition into biology and biotechnology[92].

10.5.3 The character of technological change

In the discussion of the strategies of big pharma and the strategies of national governments it has been difficult not to include explanations related to technology. To some part this is due to the interrelatedness of these theoretical entities, however, it is also symptomatic for the characteristics of the R&D intensive pharmaceutical industry: science, technology and innovation are at the core.

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. It is also such factors that to a large extent may 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 one partial explanation to the distribution of big pharma R&D units in more detail.

10.6 The molecular biology revolution

The survival of a firm in the R&D intensive pharmaceutical industry ultimately depends on its ability to find new cures. Innovation within the sector was initially dependent on knowledge in chemistry. The method 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 cures at large-scale production level. 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.[93]

The public funded research projects that took off following the end of World War II continued during the 60's and 70's 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 for finding drugs. This method, called 'rational drug design', emphasized 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.[94]

[92] Malerba & Orsenigo, 2002, pp. 667-703
[93] Ibid.
[94] Ibid.

Sometime in the early 70's universities and other public 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 it assisted in the search for small molecules. Following the shift from chemistry to biology entry barriers were broken and new players could enter the field of pharmaceuticals. These firms are referred to as *biotechs* and they profited from the close relations to the universities and institutions from which the new knowledge had been produced.[95]

Despite their advantage in knowledge of biological processes over large pharmaceutical firms, biotech firms lacked the competence and resources to successfully put drugs out on the market. The large pharmaceutical companies in contrast had such abilities but lacked understanding of genetics and biology.[96]

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[97]. Regardless of strategy the big pharma of today is involved in both intensive collaboration and acquisitions of biopharmaceutical firms.

10.6.1 Hypothesis

The trend in the pharmaceutical industry is toward 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 the 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 increasingly has become more scientific.

Since big pharma need to develop drugs for their 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 recently has not been other and perhaps more important reasons for locating close to areas with biotechnological strongholds.

[95] Cockburn, 2005, pp. 10-22.
[96] Galambos & Sturchio, 1998, pp. 250-278.
[97] Ibid., pp. 254

Conversely, should this hypothesis prove to be false there may be reasons to believe that advances in molecular biology have not had such effects in Europe. However, there may be other explanations too. For example historically located R&D units may be in proximity to biotechnological strongholds because there have been other advantages of locating prior to the molecular biology revolution.

10.6.2 Method

To be able to test this hypothesis there is a need to define *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"[98]. Cooke identifies three such locations in Europe namely Stockholm-Uppsala, Munich and Cambridge[99]. The common characteristic is that such places have acclaimed universities in biotechnology.[100]

The Milken Institute[101] carried out a comparison between universities globally and ranked these according to an index which was supposed to capture strong biotech research centres by the number of publications, the concentration of publications (how many publications that were written within a specific subfield of biotechnology) and the 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 European universities presented in figure 22 were identified among the 50 top scoring 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

Figure 22: ***Top ranked European Universities***
(Source: Milken Institute, Mind to Market: A Global Analysis of University Biotechnology Transfer and Commercialization)

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 prior to or after the study was undertaken. However we shall assume that the performance during the time of measure (1998-2002) is linked to strong performances in the past. This assumption is based on the notion that knowledge accumulates and that research performance usually can be traced

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

back to prior efforts[102]. 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 units 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 as the 127 units with dynamic data. Naturally, leaving out roughly 25% of the total data and expecting it to 'behave' as 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 70's and was established during the 80's[103]. Although the choice is somewhat arbitrary recent units will be regarded as 'recent' units from the 80's up until today. To give further detail to the investigation and because it is not completely 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 80's (for units located between 1980 and 1989), 90's (for units located between 1990 and 1999) and 00's (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 exactly at what distance such externalities are outplayed. In this study proximity will be counted at a maximum distance of 50 km between the specific university and the R&D unit. This choice of definition is a bit arbitrary, however, it is mostly cities and its suburbs which traditionally have been assigned such cluster-like qualities and these can usually be circumscribed within a circle of radius 50 km[104].

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

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

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)*

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

Explanation: *Historical* refers to R&D units being established prior 1980. *80's* refer to R&D units located between 1980 and 1989, *90's* refer to the period 1990 to 1999 and *00's* refer to the period 2000 to 2007. The number of R&D units within 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.

Out 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 UK) the numbers are 60% (52/83).

10.6.3.1 UK

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

Figure 24 shows the percentage of these R&D units in different time frames (Historical, 80's, 90's and 00's) that are located within 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.

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%**

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

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

Thus, for all big pharma R&D units located within UK; 49% (19/39) are located near University of London, 18% (7/39) are near University of Cambridge and 8% (3/39) are near University of Oxford. None of the other universities have R&D units within 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). Out of these only slightly more than half of the units (16) have dynamic data assigned to them. Eight of these units have been located historically, two during the 80's, one during the 90's and four since 2000. In the same fashion as figure 23 figure 25 summarizes location toward strongholds within 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%**

Figure 25: ***Big pharma R&D units location in reference to biotechnological strongholds over time (in France).***
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. For eight of these units the year of establishment has been determined. Four of these units are located historically, three were established during the 90's and one in 2003.

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**

Figure 26: ***Big pharma R&D units location in reference to biotechnological strongholds over time (in Switzerland)***
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 have been located historically and one in the eighties. There are no locations with unknown year of establishment.

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

Figure 27: ***Big pharma R&D units location in reference to biotechnological strongholds over time (in Sweden)***
Explanation: For further information see explanation of figure 23.

10.6.3.5 The universities

Figure 28 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[105].

[105] DeVol et al., 2006.

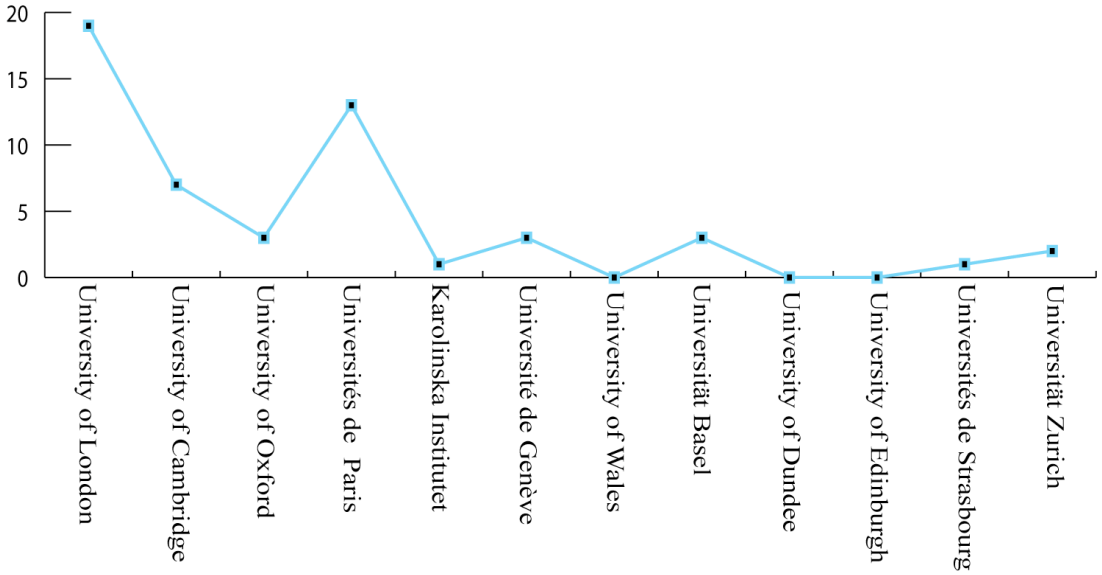

Figure 28: ***The number of big pharma R&D units in proximity to each of the biotech strongholds.***

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. In Switzerland and Sweden no such trend can be seen. On an aggregate level the trend is greatest between the 90's and 00's for countries with strongholds.

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

Furthermore, location of big pharma show 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 within 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 within proximity. Overall it seems like big pharma are drawn toward 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[106]. 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).*[107]

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' into these region has been facilitated. In the case of Cambridge, as we have seen, the movement has consisted of new openings. In Stockholm-Uppsala, the movement, possibly by ventures and collaborations, is not visible in our results.

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

Figure 29: ***Regional Biotech Comparison***
(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 at biotechnological strongholds; however, this trend is far from strong 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 UK and France, strongest when the university is embedded into a large city. Indeed, the five largest agglomerations of big pharma R&D units lie near London, Paris, Brussels, Madrid and Amsterdam (see figure 30).

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

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

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

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

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

Furthermore and already mentioned[108], location should to a considerable degree be understood 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 conflicting needs at stake too such as the need of 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 to test this hypothesis. Biotech strongholds were defined by the ranking of 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 perhaps include other factors as well. Furthermore, it is largely unclear whether big pharmas gain from any of the externalities in these milieus by

[108] Hayter, 1997.

means of locating R&D units there. Moreover, the data on the selected universities were only based on recent performance.

Another problem has been the limited information on dynamics. Indeed, the 42 R&D units without any information on the year established has the 'power' to disqualify some of the trends seen. Furthermore these R&D units do only capture some of the business activity of big pharma. As the pharmaceutical industry seem 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 its linkages. However, due to the complexity, size and discretion in some of the network linkages such a complete mapping would be difficult to accomplish.

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 seem to follow the influences of TNCs, nations and technology. However such trends are difficult to isolate following the low number of locations and the absence of any appreciation of the size of these units.

In this chapter the revolution in molecular biology 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[109] are questioning the future of the big pharma business model. Possibly in the future big pharma would need to adjust more sternly than they have done so far. Naturally such adjustments would have tremendous effects on the geography of big pharma R&D in Europe. At the end of this paper these possible future changes will be discussed in more detail.

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

11 Clusters$^{\Omega}$

This case study benchmarks four clusters environments[110], namely: Massachusetts, Ireland, Singapore, and Switzerland. The clusters were selected based upon the high concentrations of companies found in our empirical data and also because these clusters 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 investments, 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 environment stability. Thereafter, the business climate of each cluster is 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 for competitive advantage. Ultimately, a comparison of the four clusters will be conducted, to indicate 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[111]. The LMA is a section with a high density of hospitals and colleges, while the Kendall Square is more famous for the number of laboratories and discoveries of biotechnology and pharmaceuticals, but the two centres are less than three miles apart. Since many of the biopharmaceutical discoveries were coming out of the academia it was normal that the industry was first established in areas nearby universities and research hospitals[112]. In the early 20th century Harvard University sold some of their properties on Longwood Area to other hospitals so that Harvard students could gain from collaboration, meanwhile MIT moved its campus to Kendall Square, and this part gave the cluster a birth[113].

11.1.2 Policy facing life science 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

[110] Cluster environment and cluster milieu will be used interchangeably.
[111] *Massachusetts BioHistory*, <http://www.massachusettslifescience.com/biohistory.htm>
[112] Massachusetts Biotechnology Council, 2006.
[113] Pricewaterhousecoopers, 2007, <http://www.masstech.org/institute/life_science/supercluster.pdf>

supports over 35% of all R&D in Massachusetts: it maintains continued development and expansion of existing clusters[114]. Several federal agencies provide funding for Massachusetts R&D, one of the most important sources of this funding is the National Institute of Health (NIH), located within the Department of Health and Human Services (HHS). In fiscal year (FY) 2005, NIH awarded Massachusetts $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[115].

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

Figure 31: ***Top NIH grantee states FY 2005***
(Source: http://officeofbudget.od.nih.gov/UI/..%5CFY05%5CMechanismTotal.pdf)

Even though California received the highest share of NIH funding, Massachusetts receives the most NIH funds per biopharmaceutical worker of any state in the nation, with $353 per capita[116].

11.1.2.2 Grant recipients

Massachusetts' NIH funding is distributed among institutions, hospitals and research organizations. Massachusetts General Hospital was the number one recipient among all institutions in the state with $287 million in R&D support, followed by Brigham and Women's Hospital with $253 million in funding. Among the colleges and universities, Massachusetts Institute of Technology (MIT) topped the list, total at number three, with $172 million, followed by Harvard University Medical School with $169 million[117].

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

The organizations in Massachusetts pharmaceutical cluster depend on funding from the federal government and private investment. Since budget for NIH funding has levelled off after doubling from 1998 to 2003, the competition for NIH funding is fierce[118]. If the decline in funding continues, it could have remarkable impact on the Massachusetts economy. For the Medical Institutions in the Boston area that provide work for more than 150,000 people and add more than $24 billion to the state economy annually[119], it is clearly that the stakes are high.

11.1.2.3 SBIR and STTR NIH grants

The Massachusetts life science clusters receive an important funding from NIH that provides a foundation for biomedical research. The life science cluster also profit from two grant programs, 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[120]. The Small Business Innovation Research (SBIR) program requires agencies with annual extramural research and development budgets higher than $100 million to reserve at least 2.5% for awards to small technology companies. The Small Business Technology Transfer Research program (STTR) qualifications are that the budget for agencies with annual extramural research must exceed $1 billion aside 0.3% for Small US high tech firms[121]. As shown in figure 32, Massachusetts received over $84 million in financial support through SBIR and STTR programs in 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**

Figure 32: ***NIH SBIR and STTR grants to Massachusetts, FY 2005***
(Source: National Institute of Health, Office of Extramural Research)

[118] Ibid.
[119] Roland, 2007. <http://www.boston.com/business/healthcare/articles/2007/03/06/funding_slowdown_worries_hospitals/>
[120] Handbook for SBIR Proposal Preparation 2007, <http://www.sba.gov/gopher/Innovation-And-Research/SBIR-Pro-Prep/ 071106>
[121] Pricewaterhousecoopers, 2007, <http://www.masstech.org/institute/life_science/supercluster.pdf>

11.1.3 Venture capital

Biomedical research requires large amounts of capital, which come from investors that understand the science and the risks associated with science. Venture capitalists are one group that fills these criteria; in 2006 they provided $1.1 billion in financial support to Massachusetts life sciences and health industries companies, a 43% raise over the previous year. Almost two-thirds ($755 million) of the funding went to the biotechnology segment with firms focusing on cancer, autoimmune disease, and diabetes, the remnants went to medical devices and equipment companies[122]. The total volume of biotechnology venture capital invested in firms by state is an excellent indicator of how investors view the state as location for biotechnology companies.

Massachusetts was second overall in receiving total venture capital financing companies, only behind California. But the increase of 43% in venture investments in 2006 exceeded the 10% growth rate for California. In general, venture capital investment in Massachusetts more than doubled between 2002 and 2006[123].

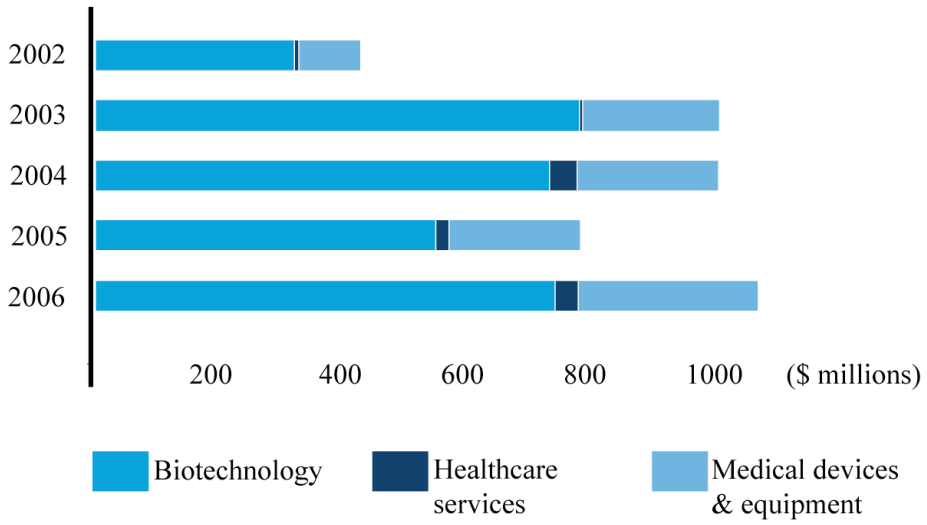

Figure 33: ***Venture Capital investment in Healthcare Industries 2006***
(Source: PricewaterhouseCoopers and the National Venture Capital Association. *Venture Capital investment in Health Industries Full Year 2006 Report, the MoneyTree Report)*

[122] 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>
[123] PricewaterhouseCoopers & the National Venture Capital Association. 2006, <http://www.pwc.com/extweb/pwcpublications.nsf/docid/CEB57559F1D0AF1D8525728F0004D828>

11.1.4 Tax cost

The corporate tax rate in Massachusetts is one of the highest among US states, namely 9.5%.[124] But the *Single Sales Factor (SSF)* method of tax distribution has significantly reduced the firms' state tax that lead up to Massachusetts becoming the most competitive state regarding state tax weight[125]. In addition to this there is also a federal corporate tax, which is varying between 15% and 39% depending on the revenues of the company.[126]

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

1. The percentage of sales that arise in the state.
2. The percentage of payroll located in the state.
3. Percentage of property located in the state.

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[127]. For the manufacturing industry the SSF method considers only the percentage of sales occurring in the state to determine the declared income to Massachusetts, and do not consider the location of property or the payroll. Here is an example to show how it works: your company sells products in all states in the USA, and you have half of the payroll and 40% of the property in Massachusetts since the majority of the facilities and your main office are located here. Assume the 2% of the products are sold in Massachusetts, and the annual profits amount to $10 million. Before SSF was adopted in Massachusetts, the state corporate income tax would be:

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

About $3.07 million of the company income would be shared out to Massachusetts for tax purpose. But after SSF adoption for manufacturers, only the sales factor determines the tax, so the calculation will look like this:

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

This makes Massachusetts an appropriate location for firms with many workers and large capital investment[128].

11.1.5 Infrastructure

Massachusetts is lacking a transportation strategy, and since it is one of the most urbanized states in the country with more than 87% of the states citizens living within an urbanized area and owning more cars per individual than the country average, Massachusetts faces

[124] MassDevelopment & the Massachusetts Alliance for Economic Development, 2003,<http://www.biotechwork.org/pages/FileStream.aspx?mode=Stream&fileId=5cd27f43-4cf4-db11-b900-00c09f26cd10>
[125] 'Corporate Tax Breaks Approved', 1995, pp. 45.
[126] *Publication 542: Corporations*, <http://www.irs.gov/pub/irs-pdf/p542.pdf>
[127] Merkowitz, 2004, <http://www.taxadmin.org/FTA/meet/re_pres04/merkowitz.pdf>
[128] MassDevelopment and the Massachusetts Alliance for Economic Development, <http://www.biotechwork.org/pages/FileStream.aspx?mode=Stream&fileId=5cd27f43-4cf4-db11-b900-00c09f26cd10>

many challenges in meeting its transportation requirements. One of the challenges is the aging infrastructure; Massachusetts has over 5,000 bridges whereof half are structurally deficient, furthermore almost 30% of the highway roads are in bad condition[129]. Another challenge is the extremely busy Logan International Airport. The airport is an important centre for processing domestic and international air cargo. It is also important for business and personal traveller, since delays are common it can cause problems[130].

11.1.6 Business climate

Massachusetts has established itself as a centre of bio-pharmaceutical research and product development. In order to quantify the presence of the big pharmas in Massachusetts, estimates are made through the identification and mapping of the big pharmas for which data has been analysed.

Totally, twenty big pharmas are located in Massachusetts, with 22 R&D units, 13 manufacturing units, and 2 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 these 10% of the total R&D and manufacturing units in the USA are located in Massachusetts according to the empirical data compiled. Big pharmas in Massachusetts are strongly focusing in neuroscience, oncology, and technologies in order to develop new medicines[131]. In addition, many smaller companies are located in the state that act on their own or in alliance with the larger companies in the development of new drugs.

The accumulation-diagram below indicates establishments of the big pharmas in Massachusetts over time. Since all founding years are not available in our empirical data, this diagram covers in total 17 R&D units and 12 manufacturing units in Massachusetts. During the time schedule that is shown in the figure, only 1 R&D unit and 2 manufacturing units has shut down in Massachusetts.

[129] Associated Industries of Massachusetts, 2002,
<http://www.massinsight.com/docs/Transition2002_TelecomBrief.PDF>
[130] *The Boston Indicators Project*,
<http://bostonindicators.org/indicatorsproject/transportation/indicator.aspx?id=1962>
[131] *Cambridge: The Brains of Biotech, the Heart of Innovation,*
<http://www.ci.cambridge.ma.us/CDD/ed/pubs/ed_biotech_broch.pdf>

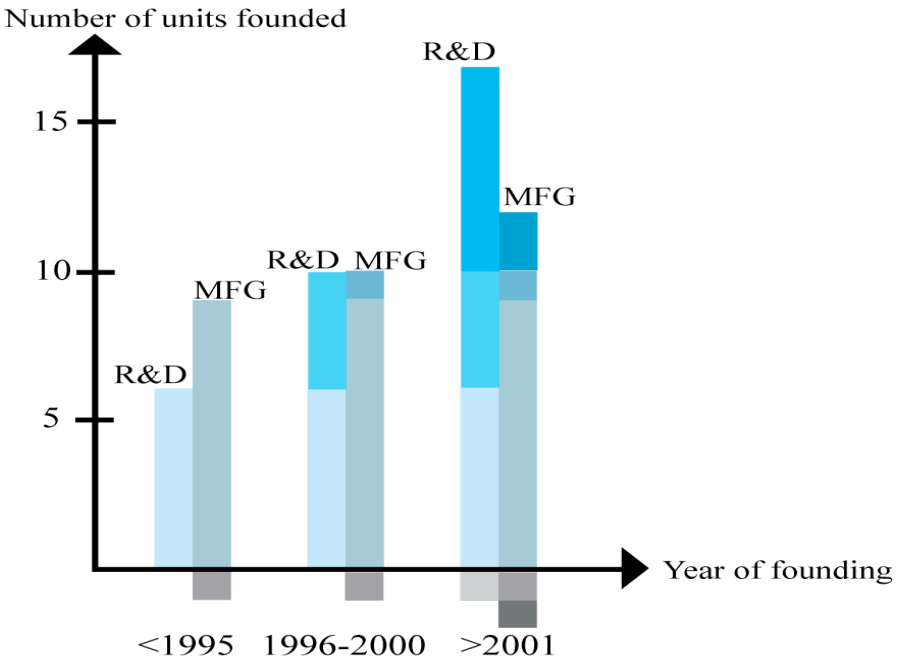

Figure 34: ***Units in Massachusetts***

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.[132]

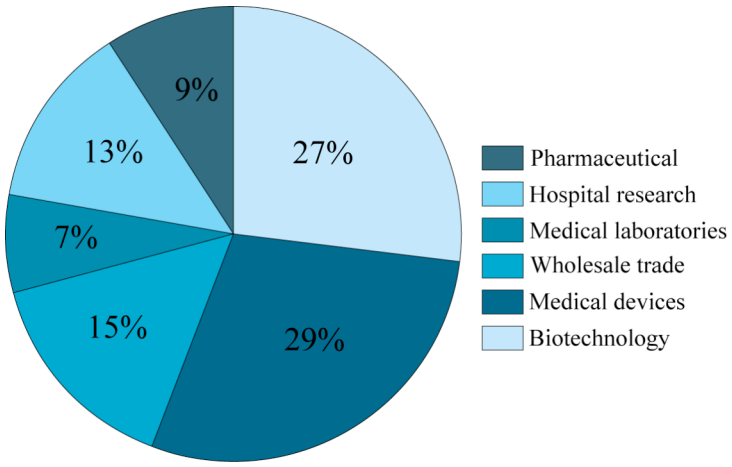

Figure 35: ***Employment in the healthcare industry in Massachusetts***
(Source: Burreau of Labor Statistics Quarterly Census of Employment and Wages, and PricewaterhouseCoopers analysis)

[132] 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 to this can 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 has the highest percentage of employees with a Bachelor's degree or higher. The focus on educated workforce has resulted in the development of the world-leading in medical research, and consequently in a number of Nobel Prize laureates from the universities of Massachusetts[133].

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, whence 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 a 51,000 m² of R&D uses, most of which are located in the sub district 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 2 million square feet of industrial companies, such as pharmaceutical and technology firms that are located here[134].

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. Benefits of industry clusters include, as mentioned in the cluster theory, good access to customers, scientific exchange between cluster companies, and a skilled workforce. These advantages are most agreed for the cluster around Kendall Square, due to the concentration of the companies and Universities Institutions[135].

11.1.7 Academia

Massachusetts academic or research institutions are playing a central role in the creation of cluster growth. In Cambridge, several of the most prominent universities in the world, such as Harvard University, that according to Academic Ranking of World Universities 2007, has been ranked number one among all universities in the world, and Massachusetts Institution of Technology (MIT) behind Harvard rated at number four in the world[136];

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[133] Sum, et al., 2006, <http://www.massinc.org/fileadmin/researchreports/labor_supply/labor_supply_full.pdf>

[134] *Concord-Alewife Rezoning Petition,* 2006, <http://www.cambridgema.gov/cdd/cp/zng/concalew/conale_guidelines.pdf>

[135] *City of Cambridge,* 2004, <http://www.cambridgema.gov/~CDD/ed/pubs/ed_policy_2004.pdf>

[136] Shanghai Jiao Tong University, 2007 <http://ed.sjtu.edu.cn/rank/2007/ARWU2007.xls>

which in year 2006-2007 had (undergraduate and graduate enrolments) student populations of 20,042[137] and 10,253[138] respectively.

11.1.7.1 Harvard and MIT

Harvard and MIT collaborate to integrate science, engineering, and medicine to explore the principles underlying health and disease, including 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, among others, biomedical imaging, bioinformatics and integrative biology, and biomedical technology[139].

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 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 move forwards the purpose of nanotechnologies to cancer research[140].

11.1.7.2 Other research centres

The Whitehead Institute is a leading, non-profit independent research institution with programs in cancer research, genetics and genomics. The research is conducted by approximately 20 researchers and more than 200 visiting scientists from around the world. Whitehead is connected to the MIT in its education activities, but totally responsible for its own research programs, and financing[141]. The institute has an annual budget of $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[142].

The Broad Institute is a research collaboration between MIT and Harvard, its associated hospitals and the Whitehead Institute, but is governed by the MIT and Harvard universities. Its purpose is to develop the potential of genomics for medicine[143]. According to MIT's news letter in November 30, 2005, 18 months after the opening of the institute in 2004, Los Angeles residents' philanthropists Eli and Edythe Broad, donated $200 million to the Broad Institute. The first donation was a $100 million gift to MIT; the additional $100 million donation went through Harvard; the combined donation will extend during a 10 years period given as $20 million per year.

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[137] *Harvard Fact Book*, 2007, <http://vpf-web.harvard.edu/budget/factbook/current_facts/2007OnlineFactbook.pdf>
[138] *MIT facts,* 2007, <http://web.mit.edu/facts/enrollment.html>
[139] *HST Research Focus Areas*, <http://hst.harvard.edu/servlet/ControllerServlet?handler=PublicHandler&action=browse&pageId=831 >
[140] MIT Center for Cancer Research, <http://web.mit.edu/ccr/about/MIT%20CCR%20FAQs.pdf>
[141] Whitehead Institute for Biomedical Research, <http://www.wi.mit.edu/about/index.html>
[142] Whitehead Institute for Biomedical Research, <http://www.wi.mit.edu/about/2006_annualrpt.pdf>
[143] Broad Institute, <http://www.broad.mit.edu/about/index.html>

McGovern Institute was established in 2000 at MIT, when Pat and Lore McGovern donated the largest gift ever to MIT, $350 million. It is a neuroscience research institute that focuses on brain disorders, with 11 researchers who conduct neuroscience research in three areas, namely perception, cognition, and action.[144]

Nearby the McGovern Institute for Brain Research, the Picower Center for Learning and Memory and the Department of Brain and Cognitive Sciences have built a new complex, opened in 2005 that will house more than 40 faculty and their research groups, located at MIT. The mission of this complex is to be the largest neuroscience research centre in the world. It offers students, both undergraduate and graduate, educational experience of a high quality and provide students to participate in research projects with leaders in their fields[145].

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

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 provides secure, furnished work spaces (including R&D) instantly, which are cost effective for minor companies, free job advertising, and also offers 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[146].

The Deshpande center was established in 2002 as a part of the MIT School of Engineering, through an initial $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 $7 million in grants. The centre supports a wide range of emerging technologies including biotechnology, medical devices, and environmental innovation etcetera[147].

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 developing 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[148].

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[144] McGovern Institute for Brain Research at MIT, <http://web.mit.edu/MCGOVERN/html/Who_We_Are/facts_at_a_glance.shtml>
[145] MIT's Department of Brain and Cognitive Sciences, <http://web.mit.edu/bcs/aboutbcs/>
[146] Cambridge Innovation Center, <http://www.cambridgeincubator.com/>
[147] Desphande Center for Technological Innovation, <http://web.mit.edu/deshpandecenter/about.html >
[148] McGovern Institute for Brain Research at MIT, <http://web.mit.edu/mcgovern/html/Areas_of_Research/mint.shtml>

11.1.9 University technology transfer

New inventions and patents are becoming a more important feature in technology licenses offered by universities. Many universities has a goal to put research results to good use, by doing this a technology transfer program has developed so that basic science and research developments get out to the public in a more efficient way. The act allows universities to take name to inventions arising from their research and to license these technologies to companies that wish to take them to market[149]. At Harvard University and MIT there are two offices that use this type of program, namely OTD and ILP.

Office of technology development (OTD) at Harvard University has a mission to make the research at Harvard more accessible outside the university, and to make the community benefit from Harvard innovations by converting their research capacity into commercial activity. OTDs goals are to commercialize Harvard research discoveries for public use, promote economic growth by serving as a bridge from laboratory to industry to translate new technologies into products that will be available to society, and patenting and licensing discoveries and inventions made at Harvard University. Companies may seek to license 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[150]. OTD grants licenses 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 licenses, OTD has established the Harvard University Technology Development Accelerator Fund. The purpose of the "Accelerator" program is to overcome what is known as the *development gap*, since new inventions that shows great promises are often at early-stage of development, and due to lack of financial support many new technologies with potential never make it out of the lab[151].

Industrial Liaison Program (ILP) was established in 1948 at MIT, it works as a linkage between university and industry; ILP join member companies with the latest research developments at MIT, and meanwhile to help the industry in supporting the MIT's research performance. A large number of companies, approximately 200 worldwide, turn to ILP for access to professional MIT researcher, and information that will help them bring innovation to market[152]. Each company that join ILP is assigned an Industrial Liaison Officer (ILO) that is familiar with the industry, and can rapidly get the importance emerging MIT technology and help the company develop ways to influence them for the business advantage. The ILO is positioned to be an effective supporter for the needs of the company, and understand what the company wants to achieve at MIT. To become a MIT ILP member, the minimum fee is $60,000 annually, and the company has to commit to a two-year membership[153].

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[149] The Association of University Technology Managers, <http://www.autm.net/aboutTT/>
[150] Harvard University Office Of Technology Development, <http://otd.harvard.edu/about/>
[151] Harvard University Office Of Technology Development, <http://otd.harvard.edu/inventions/acceleratorfund/>
[152] Office of Corporate Relations and the Industrial Liaison Program, <http://ilp-www.mit.edu/display_page.a4d?key=P2>
[153] Ibid.

11.2 Ireland

11.2.1 History of the life science sector

In the late 1950's 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, in order to ensure access to a skilled work force that could manage to work in the new high tech firms[154]. Through the work of the Industrial Development Authority (IDA) in the 1970's, the pharmaceutical industry expanded; attraction of foreign companies and employment grew markedly, from 1,300 in 1972 to 4,750 in 1979 in the pharmaceutical sector. During the 1980's pharmaceutical companies in Ireland focused on manufacturing. The growth of life science led to both expansion of existing firms and attraction of new companies[155].

11.2.2 Policy facing life science in Ireland

The major programmes involved in the foundation of life science in Ireland are SFI's, and HEA's programme. Both of these initiatives have the aim of leading to a rapid progress in establishing of 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 is playing a central role for the national innovation. Some of the universities that are funded by HEA are University College Cork, University College Dublin, and National University of Ireland. Research programmes that are funded by the HEA support collaboration between institutions and between disciplines in research for the benefit of Ireland. The range of HEA funding activities in the research system are:

- The HEA provides the necessary grants for research funding
- The Programme for Research in Third-Level Institutions (PRTLI) supports large research programmes and infrastructure
- 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 €605 million has been allocated to the institutions whence €295 million to the bio science sector and some 37% of the total amount has been expended by 2003[156]. The funding is distributed among several universities; University College Dublin is awarded €35.9 million,

[154] RecruitIreland, <http://www.recruitireland.com/careercentre/focuspharma.asp>
[155] van Egeraat, 2006,
<http://www.nuim.ie/nirsa/research/documents/WP%2028%20Chris%20van%20Egeraat.pdf>
[156] Higher Education Authority, <http://www.hea.ie/index.cfm/page/sub/id/543>

University College Cork is awarded €62.6 million, National University of Ireland is awarded €28.8 million, and Trinity College Dublin is awarded €46.2 million[157].

11.2.2.2 Science Foundation Ireland (SFI)

SFI is an organization 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 €184 billion NDP[158] 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 provides among others €54.6 billion for investment in economic infrastructure, €25.8 billion for human capital such as schools and higher education, and €20 billion for enterprises, science and innovation whence €6.1 billion of them will go to Science, Technology, and Innovation[159]. Totally, €8.2 billion has been allocated for scientific research under the NDP and SSTI of which €1.4 billion is SFI's responsibility to invest. SFI offers grants to researchers who wish to relocate to Ireland and those who are already based in Ireland[160].

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 affects the Irish economy, and expand educational and career opportunities. Strategic Research Cluster (SRC) is a programme that links scientists from academia and industry to central research questions, and affect the development of Irish technology companies. [161]

11.2.2.3 Industrial Development Authority (IDA)

IDA is the Irish Government agency supporting inward investments and is actively seeking to attract investments from abroad in manufacturing and internationally traded service segments. IDA also encourages companies to expand their current investments in the country. During 2006 IDA invested in 54 R&D projects, involving almost €470 million. The supported companies spent approximately €15 billion in Ireland during 2006, whence €2.8 billion was paid in corporation tax. In 2006, over 50% of employments in IDA supported projects had wages and salaries levels of €40,000 annually[162].

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, developing professional standards etcetera. Outgoings on R&D by IVCA supported high technology companies represents 23% of total Irish spend on Business Expenditure on

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[157] Higher Education Authority, <http://www.hea.ie/index.cfm/page/news/sub/755/section/NewsRelDetails/key/186>

[158] 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.

[159] *Ireland National Development Plan* 2007-2013, <http://www.ndp.ie/documents/ndp2007-2013/NDP-2007-2013-English.pdf>

[160] Science Foundation Ireland, <http://www.sfi.ie/content/content.asp?section_id=207&language_id=1>

[161] Science Foundation Ireland, <http://www.sfi.ie/uploads/documents/upload/SFI_Brochure.pdf>

[162] Industrial Development Agency, <http://www.idaireland.com/home/index.aspx?id=8>

Research and Development (BERD). In 2005 IVCA supported technology firms with €89 million for R&D, an increase of 34% since 2004[163]. The funds active in life sciences investment are ACT Venture Capital that has completed over 70 investments, principally in technology based companies, and the first science venture capital firm in Ireland, Seroba BioVentures that invest in pharmaceutical, biotechnology has a target size of up to €25 million[164]. In 2002, Seroba BioVentures had already completed a first closing of €15 million[165].

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 €95 million through Enterprise Ireland to partner with the private sector to maintain the progress of the venture capital market[166].

11.2.3 Tax cost

The total corporate tax in Ireland is the lowest among all EU member countries, see figure 36 below. The corporate tax rate is 12.5% since 1 January, 2003, and is charged on the profits, i.e. business income, investment income and capital gains, of a company[167]. Until 1998 the corporate tax was 32% in Ireland, between 1999 and 2003 the rate fell in stages, as a result of an agreement between the Irish Government and EU. For every year the rate fell with 4% till 2002, and thereafter the rate has been 12.5%. The previous 10% *Manufacturing Rate of Corporation Tax* that applied to companies manufacturing goods in Ireland, or selling goods which are manufactured within Ireland by a 90% subsidiary, is still available until 2010 and then the final 12.5% rate will come into effect[168].

[163] The Irish Venture Capital Association, 2005, <http://www.ivca.ie/eis_2005.pdf>
[164] Seroba BioVentures, <http://www.seroba.ie/seroba/Main/Splash.htm>
[165] Seroba BioVentures, <http://www.seroba.ie/seroba/Main/2002.htm>
[166] Enterprise Ireland, <http://www.enterpriseireland.com/Grow/Finance/VentureCapitalists.htm>
[167] Ireland Development Agency, 2007, <http://www.idaireland.com/uploads/documents/IDA_Publications/Guide_to_Tax_in_Ireland_07_Final.pdf>
[168]LowTax Network, <http://www.lowtax.net/lowtax/html/jirdctx.html>

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

Figure 36: ***Corporate tax rates***
(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 with the purpose to encourage an increase in the amount of both foreign and domestic companies to start up new and/or additional R&D operations in Ireland. The R&D tax credit is in addition to the corporate tax deduction available at 12.5%, and applies to companies that own at least 50% of the company[169]. The company must also acquire expenditure in carrying R&D operations in the European Economic Area (EEA)[170]. The expenditure must be tax-deductible only in Ireland, be investigative in a field of science or technology, and available in a limited way to universities or institutes of higher education[171].

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 pharmas, there are in total, 8 R&D units whence 3 in Cork, and 2 in Dublin, and 40 manufacturing units whence 13 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 unit. 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[172].

[169] Ireland Development Agency, <http://www.idaireland.com/home/index.aspx?id=681>
[170] EEA includes EU-27 plus Norway, Iceland and Liechtenstein.
[171] 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>
[172] Pharmacareers, 2007, <http://www.pharmacareersireland.com/gpage5.html>

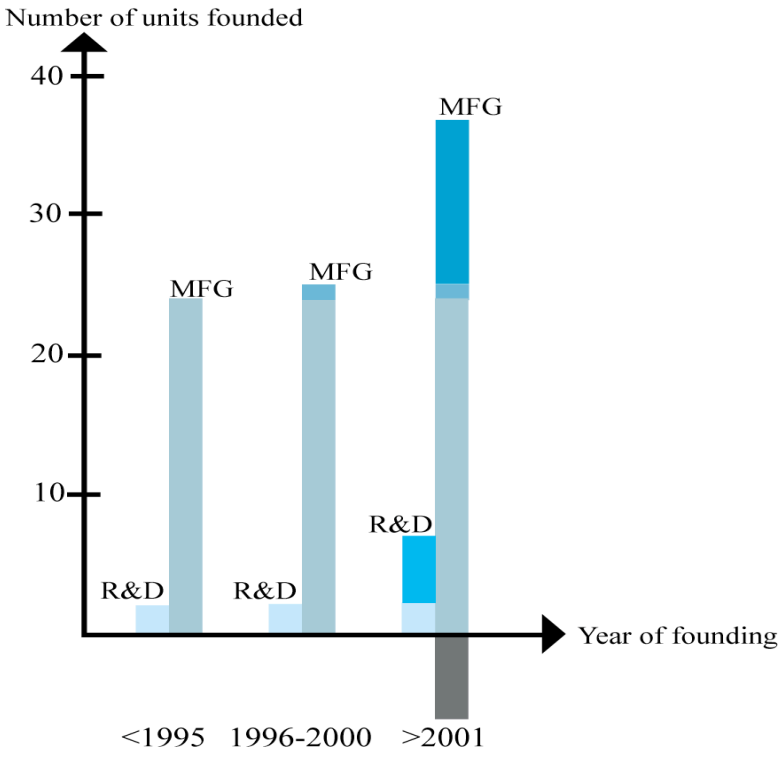

Figure 37: ***Units in Ireland***

As presented above, Ireland is attracting mostly manufacturing operations. During the time-period given in the diagram the manufacturing units have increased markedly, also R&D units have increased. Three big pharma manufacturing operations have shut down in just a couple of years. The figure shows establishments of operations with known founding year; there are 3 establishments of manufacturing units that 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 today, including big pharmas, 83 pharmaceutical facilities, with more than 17,000 employees in Ireland. In 2003, the two counties of Cork and Dublin estimated for 45% of all employment in pharmaceutical manufacturing. In the life science industry, Ireland has over 170 companies were 35,000 people are working in the pharmaceutical, biotechnology, and medical devices sectors[173]. The unemployment rate is of 4.4% that is amongst the lowest within EU[174].

11.2.5 Infrastructure

A well functioning infrastructure in a country affects competitiveness in several ways; it can reduce traffic congestion, delivery times, and increase consumer choice. Investment in

[173] Ireland Development Agency, <http://www.idaireland.com/home/index.aspx?id=64>
[174] Ireland Development Agency , 2007, <http://www.idaireland.com/uploads/documents/IDA_Publications/Vital_Statistics_FINAL_May_2007_formatting_correct__4_.pdf>

the infrastructure has not kept up to speed with the economic growth in Ireland. The traffic in Ireland is heavy, the broadband access is inadequate, and the waste removal has room for improvement. According to OECD statistics, when comparing Ireland to other countries referred to overall infrastructure, the ranking is one of the lowest, more specific Ireland ranked 22nd out of 25 in 2006. These rankings reflect deficits which need to be tackled. The National Development Plan 2007-2013 provides €54.7 billion for investments in infrastructure. The investment in transport infrastructure will in total be €33 billion, with main focus on building new national roads, public transport, and improving national airports[175]. Another issue in Ireland is the industrial electricity prices; they increased with 52% between 2002 and 2007, but meanwhile electricity prices increased in other EU countries as well. In Ireland, to solve this problem the Commission for Energy Regulation (CER) has announced that there will be an electricity price reduction of 4.4% for small business consumers and 8.4% for medium business consumers, from 1 November 2007. [176]

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 till year 2020, which has a purpose to build a successful Cork in terms of maintaining a well-qualified workforce, the development of *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 of which are involved in similar enterprises; this strategy supports academia, venture capitalists, and other parties to come together, fostering greater innovation. Investors in the pharmaceutical and healthcare, and information and communication technology sectors is proof of the clustering strategy when making Cork their location, and it can be seen since Ireland has the third largest concentration of pharmaceutical companies in the world due to 13 top big pharmas are located here[177].

11.2.6.1 Academia in Cork

University College Cork (UCC) has a commitment to excellence, its undergraduate and postgraduate programmes have contributed to both the pharmaceutical and biotechnological success in the region. Evidently, information technology is strong in Cork, particularly the computer science department at UCC that is the largest growing section in the university with approximately 1260 students. The Cork area is also home to manufacturing services of most of the international pharmaceutical companies. Clearly, UCC is an important source to highly skilled students; in 1998, UCC initiated BSc Degree programme in pharmaceutical chemistry. The university ensures that students are integrated into the pharmaceutical sector

[175] Ireland National Development Plan 2007-2013, <http://www.ndp.ie/documents/ndp2007-2013/NDP-2007-2013-English.pdf>
[176] Forfas, 2007, <http://www.forfas.ie/publications/forfas071112/overview_infrastructure_issues_2007.pdf>
[177] Cork City Council, 2005, <http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf>

after their education. During 2003, the university started a new pharmacy degree programme which focuses on scientific and clinical regulations[178].

The links between UCC and the industry have made Ireland a good base for the research. During 2002-2003, the gross income of the university from councils for scientific evaluations, so-called peer-reviewed sources, surpassed €44 million. These research activities have been supported by the university through €100 million in funds investment from the National Development Plan. The university has a goal to maintain the position in this area, during 2004-2005 the research income was approximate €46 million; since 2000, UCC has been accepting €70 million for more than 30 research programmes financed by Science Foundation Ireland (SFI). These include the Bioscience Institute focusing on cancer & cell signalling, and neuroscience, analytical and the Biological Chemistry Research Institute that investigate the design and development of new pharmaceutical agents, and the National Microelectronics Research Centre, which focus on research within optoelectronics, and nano-scale science and technology[179]. Another major collaborative research project into gastrointestinal diseases that GlaxoSmithKline (GSK) established in UCC, is jointly supported by IDA Ireland and SFI, and involving up to €13.7 million. Researchers from GlaxoSmithKline's Gastrointestinal Centre, works closely with researchers at UCC, to identify new drug targets for the treatment of bowel disease. Such research projects involving a high-level of collaboration between one major pharmaceutical company, and one of the top universities in Ireland, represents the government strategy to promote industrial-academic collaborations[180]. In 2005, UCC received totally €62 million from different sources, such as European Union, Government Departments, SFI, and industry etcetera. The industry contributed with approximately €6 million[181].

Cork Institute of Technology (CIT) offers courses in Science, Computing, Business, and Engineering etcetera. 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. The institute offers like many others, postgraduate research programmes, likewise since the Institute includes specialist technology Centres that receives funding from EU, and industry sectors, expertise and advice can be offered too[182].

11.2.7 Innovation milieus

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

[178] Ibid.
[179] Ibid.
[180] Ireland Development Agency, <http://www.idaireland.com/home/news.aspx?id=9&content_id=608>
[181] University College Cork, *Research at UCC,* 2006, <http://www.ucc.ie/en/ResearchandIndustry/OfficeoftheVPforResearch/Research/DocumentFile,16285,en.pdf>
[182] *Strategic Cork*, 2005, <http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf>

The Knowledge Zone is located in the south west of Cork, being aware of that proximity is important for knowledge-based companies. The zone offers companies an opportunity to locate nearby the city spaces of learning so that they can create strong relationships and share knowledge with researchers and other high skilled persons. This idea is about eliminating barriers so that ideas and innovation flows, to create economic development in Ireland[183].

The National Microelectronics Research Centre (NMRC) is an information and communications technology (ICT) research institute within UCC, which is involved in a number of research projects at both national and international stage. 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, micro technologies, and photonics. The Irish ICT segment is the largest single manufacturing sector in Ireland. Together with the industry and the government agencies, the Irish economy and research will develop to make NMRC more powerful than it is today[184].

11.2.8 University technology transfer

Technology Transfer Initiative (TTI) is a project co-funded by the participating universities, Enterprise Ireland, under the National Development Plan 2000-2006. TTI is helping 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 communication technology (ICT), engineering, and food. TTI can also enhance the information and assistance to companies engaging in R&D[185].

NovaUCD, started in 2003, is a €11 million Innovation and Technology Transfer Centre in University College Dublin. NovaUCD has a goal to become one of the worlds leading commercializers of research activity. Today, NovaUCD is in charge for the commercialisation from 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[186].

[183] *Strategic Cork*, 2005, <http://www.corkcity.ie/strategiccorkguide/competitive_edge/innovation_and_entrepreneurship.shtml>
[184] *Strategic Cork*, 2005, <http://www.corkcity.ie/strategiccorkguide/pdf/download/Eng_CRKGUIDE.pdf>
[185] University College Cork, <http://www.ucc.ie/en/ResearchandIndustry/OfficeoftheVPforResearch/IndustrialLiaisonandTechnology/Transfer/TechnologyTransferInitiative/>
[186] University College Dublin NovaUCD, <http://www.ucd.ie/nova/>

11.3 Singapore

11.3.1 History

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

In the 1970's unemployment was not a problem anymore, the EDB started export oriented industries, and marketed Singapore as a start-up location with workforce available. The industry in Singapore widened, there were no longer only wood products, or toys 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."*[187] To attain what the minister delivered, the EDB renewed importance on manpower development through the science park that was set up next to the National University of Singapore to stimulate research and development activities, and also establishment of institutions of technology jointly with the governments of Japan and France. During 1980's and 1990's Singapore 7,000 multinational companies were established in Singapore, and the cluster development begun[188].

11.3.2 Policy facing life science in Singapore

In Singapore the ambition is to become a centre for knowledge, talent, and business. To achieve this goal, government grants helps 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 receive grants from two main sources, namely the Agency for Science, Technology and Research (A*STAR) and the Economic Development Board (EDB).

11.3.2.2 A*STAR

A*STAR has a mission 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

[187] Singapore Economic Development Board, <http://www.edb.gov.sg/edb/sg/en_uk/index/about_us/our_history.html>
[188] Ibid.

biomedical research and development in Singapore. The BMRC strengthen fields such as pharmaceutical, medical devices, biotechnology, and healthcare services within the biomedical field and the SERC strengthen electronics, chemical, and engineering clusters. From its start in 2000 till 2005, BMRC has awarded 264 extramural grants that run up to about $195 million in research funding[189]. The SERC grants, averaging $500,000 per project, are awarded to research projects covering areas including electronics, chemistry, physics etcetera. The funding period is typically three years; in 2001 a total of $8.04 million was granted to 16 projects[190].

11.3.2.3 EDB

EDB is the lead government agency providing investments to stimulate the domestic economy. EDB focuses on the manufacturing and its services, and exportable services sectors. In 2005, EDB distributed $100 million to attract investments in the manufacturing sector, these investments contributed to 18,000 jobs, of which approximately 70% was skilled jobs[191].

A part of EDB is the Business Angels Scheme (BAS) that provide capital for start-up companies or innovative firms that are less than five years old and developing new products. The BAS invests up to $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 $300,000, but the investor must put in at least $75,000 and the start-up company have to be incorporated for less than three years in Singapore. For small companies with less than 10 employees, the Micro Loan Programme provides loans up to $50,000 at fixed or variable rates[192].

For the R&D sector the government invested $660 million in 2005 to strengthen the R&D potential of Singapore. Of the $660 million, $543 million went to the public sector research in areas such as science, engineering, and biomedical sciences. For the private sector $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[193].

11.3.3 Venture capital

The private sector investment in venture capital is not yet well developed in Singapore. Today, more than 150 venture capital companies are located in Singapore; together they contribute $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

[189] Singapore Economic Development Board, 2005, <http://www.sedb.com/edb/sg/en_uk/index/news_room/news/2006/biomedical_sciences.html>
[190] Agency for Science, Technology and Research, 2006, <http://www.astar.edu.sg/astar/about/action/pressrelease_details.do;jsessionid=A44ADA6104FA7E8BB3669F9A51064D1A?id=0e0d5538216u>
[191] Singapore Government, <http://www.mof.gov.sg/budget_2005/expenditure_overview/mti.html>
[192] Singapore Government, <http://www.spring.gov.sg/Content/WebPageLeft.aspx?id=b859b2c6-093a-4e75-9f0e-1c5bf2792a9c>
[193] Singapore Government, <http://www.mof.gov.sg/budget_2005/expenditure_overview/mti.html>

Europe, and the remaining 35% are from Asia[194]. 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 the industry growth. To do this, SVCA facilitate link between firms seeking finance with venture capital companies and interaction among professionals in the venture capital and private equity industry[195].

11.3.4 Tax cost

The corporate taxes are being cut in many countries, especially in Europe. In order to help and keep Singapore attractive as a business location, the corporate tax rate will be reduced from 20% to 18% in 2008[196]. With the current 20% corporate tax being higher than some competing countries, such as Ireland with 12.5%, this corporate tax cut will enhance the competitiveness of Singapore as a business location.

Today, for new start-up companies, there is a zero tax for the first three years of incorporation, thereafter there is a partial tax exemption with 5% rate for the first $10,000 of income and 10% for the next $90,000. As from year 2008, there will be a zero tax rate for the first three years or for the first $100,000, and thereafter a 9% tax rate on annual profits for the next $290,000. For existing companies with $10,000 income, there will be a 4.5% tax rate, as from year 2008, and thereafter 9% tax rate for the income up to $300,000[197], see figure 38.

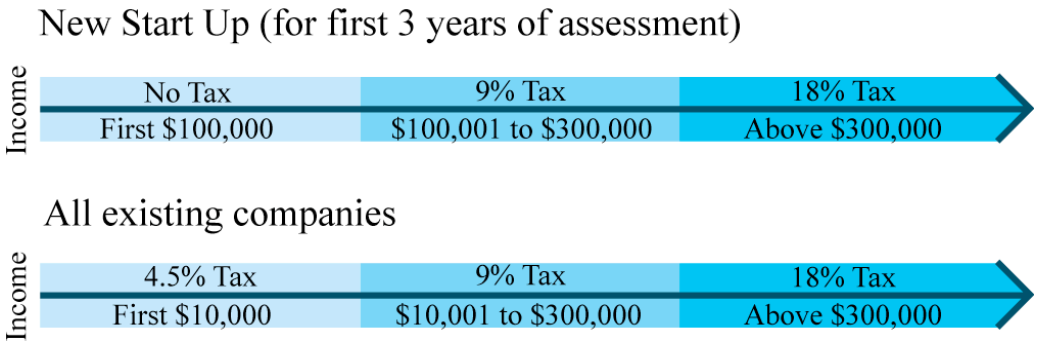

Figure 38: ***Singapore corporate tax***
(Source: http://www.mof.gov.sg/budget_2006/budget_speech/subsection6.2.html)

[194] Singapore Economic Development Board, 2002, <http://www.sedb.com/edb/sg/en_uk/index/news_room/news/2002/speech_by_mr_teo_ming0.html>
[195] The Singapore Venture Capital and Private Equity Association, <http://www.svca.org.sg/about1.htm>
[196] International Enterprise Singapore, <http://www.iesingapore.gov.sg/wps/portal/!ut/p/kcxml/04_Sj9SPykssy0xPLMnMz0vM0Y_QjzKLN4g38nAHSYGYjvqRMJEgfW99X4_83FT9AP2C3IhyR0dFRQBOc5AF/delta/base64xml/L3dJdyEvd0ZNQUFzQUMvNElVRS82XzlfMUZC>
[197] Singapore Government, 2006, <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 repetitively been named the best airport in the world. It serves more than 60 airlines to over 145 cities and it provides speedy and unproblematic clearance. For arriving passengers it takes totally 30 minutes to clear immigration, claim their baggage, and pass customs procedures.

For the public transport, such as the buses, they start from 5:30 AM to midnight, every 5 minutes during rush hour and every 10 minutes at off peak time. About 80% of the buses have air conditioning and almost all are new or in good condition. The local train network has 51 stations across the country, and recently they have started operating to Changi Airport, which makes it very convenient for business people, but also for tourists. The local train also starts at 5:30 AM up to midnight[198].

11.3.6 Business climate

Singapore has set its sights on becoming the life science centrality for the Asia Pacific region, because of 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 8 R&D units, and 14 manufacturing units of the big pharmas 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 establish themselves in Singapore. From 2001 and forward the number of manufacturing units has almost tripled 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.

[198] Singapore Mirror, <http://www.singaporemirror.com.sg/ab_infr.htm>
[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>

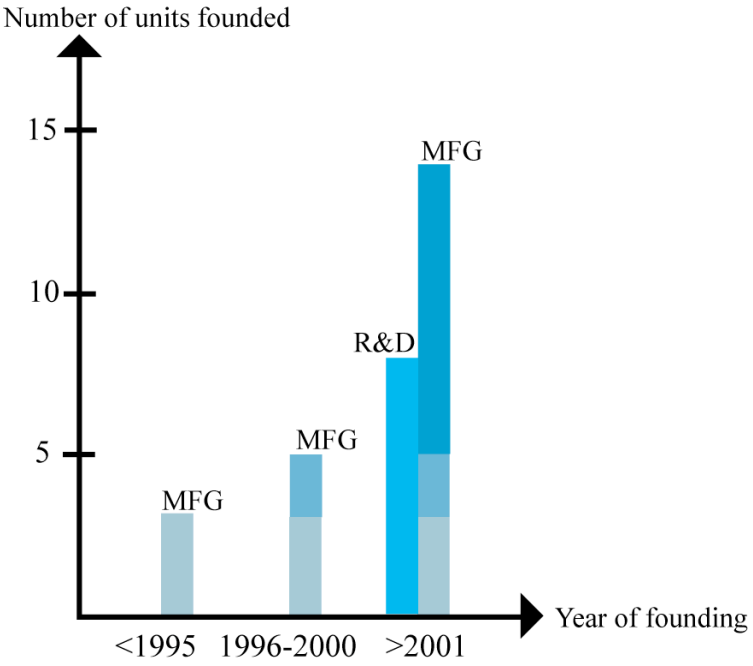

Figure 39: ***Units in Singapore***

The economy of Singapore grew by 7.9% in 2006 and the total employment expanded by 7.6%, e.g.176, 000 jobs were created. Between January and September 2007, 171,500 new jobs were created in Singapore, almost the same amount job creations for the whole year of 2006; meanwhile the unemployment rate fell from 3.1% in 2005 to 1.7% in 2007, the lowest rate since 1996[201]. In Singapore there are approximately 2.0 million workers, whence 10,571 people are working within the biomedical sector. Of the total 10,571 workforce in the biomedical field 4,020 are working within the pharmaceutical sector and the remaining 6,551 people are working 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 universities[203]. Nanyang Technological University is a research-intensive university in Singapore with 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 them is

[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>
[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>

collaboration between NUS, MIT, and the 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 that investigate dietary and other environmental determinants of chronic diseases. The study has been supported since 1993 by the National Cancer Institute, in the USA, and so far it has been granted about $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 have been established to ease location and provide common facilities for start-up companies with focus 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 organizations, and biomedical universities, such as the National University of Singapore and National University Hospital. The Biopolis complex is home to more than 2,000 researchers and technicians, and till the end of 2009 an additional 74,000 m^2 of space will be completed for building up world-class research area. Five of nine buildings accommodate A*STAR's research institutes such as the Institute of Molecular and Cell Biology, the Genome Institute of Singapore and some more. 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].

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 for supporting manufacturers with an environment providing power, water, telecommunication, and gas requirements available in the park. Through its fully supplied infrastructure, TBP addresses the needs of biomedical manufacturing companies. Today, TBP occupies an area of over 360 hectares and some of the worlds leading pharmaceutical companies are located there, namely GlaxoSmithKline, Merck, Pfizer and many more; these companies can by locating there 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

[205] National University of Singapore, 2003,
<http://www.nus.edu.sg/ore/publications/quest/03_Research%20Collaboration%2019-26.pdf>
[206] International Enterprise Singapre, <http://www.biomed-singapore.com/etc/medialib/
bms_downloads/newsroom.Par.0010.File.tmp/BIOTECH%200708.pdf>
[207] Singapore Government,
<http://www.jtc.gov.sg/portfolio/tuasbiomedicalpark/fast%20facts/pages/index.aspx>

for start-up enterprises, by teaching, training, and internship talented people. This is done by the support of NUS Overseas Colleges (NOC), Industry Liaison Office (ILO), and NUS Entrepreneurship Centre (NEC). NOC offers an education 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

The Genome Institute of Singapore (GIS) , set in the Biopolis is provided with $167 million research grant, mainly from A*STAR, to integrate new technologies to identify novel genes and molecular targets in diseases that are common in the Asia-Pacific region, mostly focused on cancer and infectious diseases. The GIS is planned to help the growth of the life science industry in Singapore, to do this GIS hired approximately 250 professional scientists between 2005 and 2007, from all around the world to make the institute competitive. One important goal for Singapore is to establish a genomic 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 in 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, global, 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 that was set up in 1992, is active in creating relationships with top universities and technological commercialization groups around the world. ILO helps to translate new discoveries by NUS researcher into new products and services via

[208] National University of Singapore, <http://www.nus.edu.sg/enterprise/aboutus/index.html>
[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>

certificating these technologies to existing or new companies. Meanwhile, ILO eases 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 industry updated of latest developments while maintaining NUS relation to its partners in industry[211].

11.4 Switzerland

11.4.1 History

The life science industry 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 sixties, when also Switzerland decided to invest a lot of money in biological research[213]. In the 1970's 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 worlds' leading pharmaceutical companies, namely 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. Many people were convinced that Switzerland, a small size country with a relatively high number of big pharmas, is an attractive location for the pharmaceutical industry[215].

11.4.2 Policy facing life science in Switzerland

The Confederation, the Swiss union of cantons, has a responsibility concerning science and technology which is performed mainly 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 State Secretariat for Education and Research (SER) agency. In 2007, SER spent CHF (Swiss franc) 1.7 billion in subsidies for different objects[216], see figure 40.

[211] National University of Singapore, <http://www.nus.edu.sg/enterprise/enterprisecluster/ilo.html>
[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>

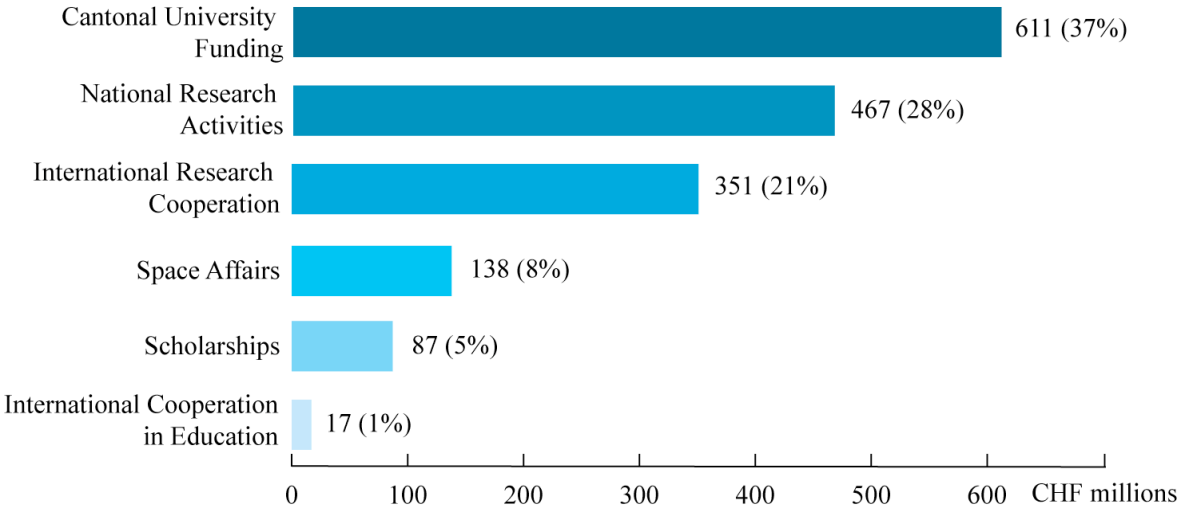

Figure 40: ***SER Subsidies in 2007 by area of focus***
(Source: http://www.sbf.admin.ch/htm/sbf/zahlen_en.html)

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, it is the only instrument for research funding. SNSF is mainly financed by the Confederation, through SER. SNSF annually supports approximately 7,000 scientists, performing basic research in various disciplines, for example philosophy, biology and medicine. In 2006, SNSF had a total expenditure of CHF 491 million in research financing; research in the humanities and social science received 25% of the grants, 35% went to projects on mathematics, natural, and engineering sciences, and 40% went to research of biology and medicine. The funding options in any discipline include: project funding, individual and career development funding, and grants toward publication costs etcetera[217].

11.4.2.2 The Commission for Technology and Innovation (CTI)

The CTI is a Swiss confederation innovation promotion agency was established in 1951, 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 finance several hundred R&D projects that companies execute in collaboration with universities. The funding is available for all disciplines. Between 2001 and 2005, almost 1,500 R&D projects were supported, and between 2004 and 2007 the CTI budget ran up to CHF 400 million. Since 1996, more than 140 start-up companies have been awarded by CTI, and today 85% of these are still in business and they have created more than 4,000 new jobs in Switzerland[218].

[217] Swiss National Science Foundation, <http://www.snf.ch/e/aboutus/seiten/default.aspx>
[218] Federal Department of Economic Affairs, retrieved 7 December 2007, <http://www.bbt.admin.ch/kti/org/00278/index.html?lang=en>

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 raised funds originated from abroad and this can indicate that Switzerland is a strong life science cluster by attracting foreign venture capitalists to venture in Switzerland and developing a domestic private industry. Domestic private equity investments amounted to €583.3 million, in 2006. Between 2005 and 2006 the funds raised amounted to €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 with 22%, and pension funds with 18.7%[219].

11.4.4 Tax cost

The Swiss taxes are among the lowest in Europe, both for companies and individuals. The effective corporate tax rate comprises federal and cantonal taxes, Switzerland has 26 states called cantons; the federal corporate income tax rate is 8.5% throughout Switzerland and in addition, each of the 26 cantons has its own separate tax rate. Today, the canton 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]. In common, all cantons offer tax relief to attract foreign companies and to encourage start-up companies. The tax relief is a form of a participation exemption that concerns Swiss companies with substantial participants, e.g. for mixed holding companies the tax relief is calculated according to the percentage of the net income from participations to the corporate total net income. To qualify for relief, the participation must represent at least 20% in the company or exceeding CHF 2 million in fair market value. For pure holding companies there is a holding privilege, almost a complete exemption from tax at the 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 fulfilled pure holding companies just pay 8.5% federal tax on the income. According to domiciliary companies, that are companies with only administrative activities in Switzerland, e.g. headquarters, with all or the major part of 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. For any traveller, they can choose between three major airports that offer direct international flights. One of these is the Zurich airport, which today presents 120 destinations over 70 countries, the two other international airports are Basel and Geneva that provides 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 worlds most compact, highways

[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>
[221] Taxation, <http://www.taxation.ch/index.cfm/fuseaction/show/temp/default/path/1-535.htm>

interconnect all parts of the country, and the highways are four-lane[222]. The public transport is of high quality. The *Swiss Travel System* is a network of trains, buses, and ships. Most of the cities are connected by the InterCity trains, but they run once per hour; for local buses the network offers daily service from 5:30 AM till midnight, every six minutes during rush hours[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 pharmas 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.

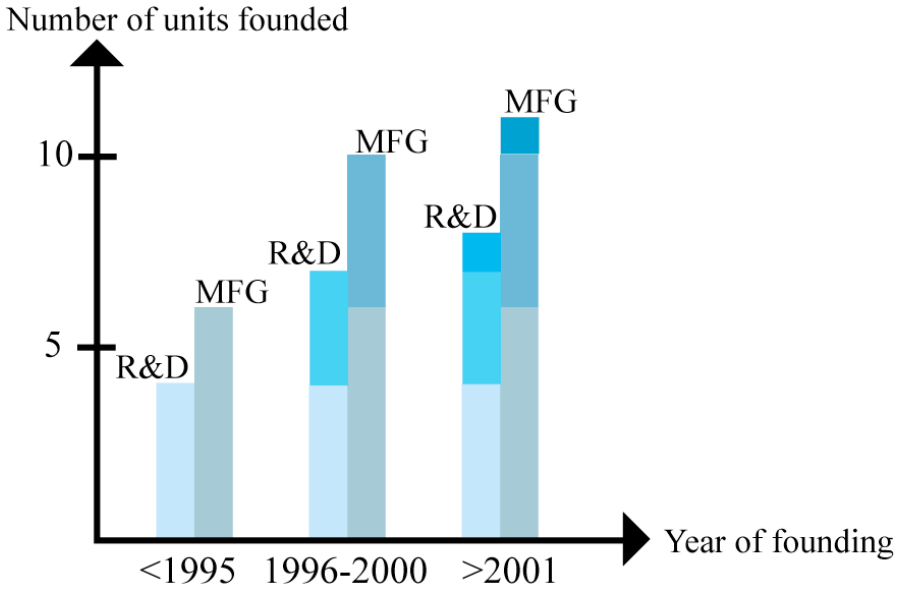

Figure 41: ***Units in Switzerland***

The accumulation-diagram above gives an overview of the establishments of big pharmas in Switzerland. Since founding years for nine of the manufacturing units and for three of the R&D units are missing, the diagram is not complete. The compiled data of big pharmas does not show any closing of plants in Switzerland.

The four main bio-pharmaceutical clusters in Switzerland included in 2006, 251 biopharmaceutical companies, more specific:

1. Bio Valley in Basel with 64 companies.
2. Greater Zurich area with 96 companies.

[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>

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 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].

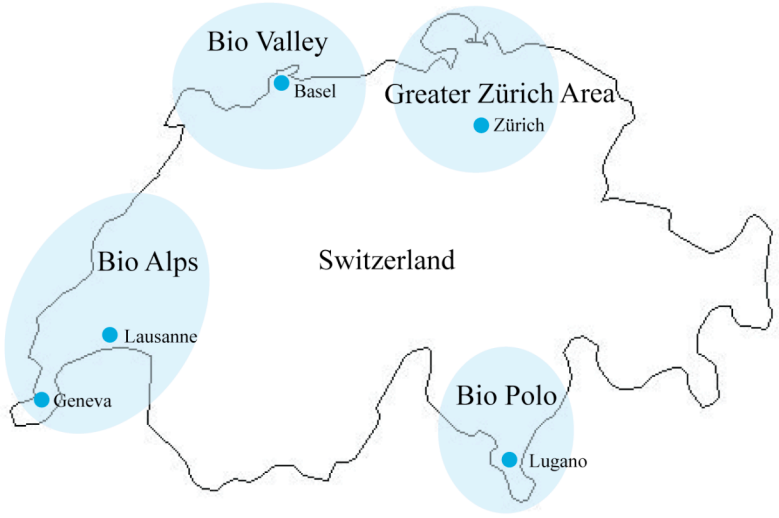

Figure 42: ***Map of Switzerland showing the clusters***
(Source: http://www.biopolo.ch/Products/Swiss%20LifeScience%20Survey%202006.ppt#2)

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 department Biozentrum opened in 1971, it is a basic research institute focused in 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

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

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 in three steps; first there is basic studies taking 4 years, whence the last year consists of practical work in research groups, secondly there is PhD studies that require 3-4 years of research, and thirdly there are postdoctoral studies, with international exchange programmes.[229]

11.4.7.2 University of Zurich

The University of Zurich, founded in 1833, 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, in total 12 Nobel Prize laureates held a professorship 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 a combination of medical care with scientific activities in research and teaching befall. As many other universities, collaborations with other universities is common, e.g. 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 organizations. The TechnoPark helps enterprises to implement new technologies, solve business problems, and access key partners. For start-up companies access to venture capitalists, business angels (private investors), and seed money providers and bankers is necessary, but with the assistance of TechnoPark it is possible to interact with them. This innovation centre is a private company that has a foundation that promotes technology transfer by a network available to science and industry. Apart from the network, it supports all technology-oriented start-up companies[232].

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[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>
[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 located in 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 that moved into the innovation centre was the new started Actelion, Discovery Technologies, and Rolic. The Basler Kantonalbank provided financial support for building up laboratories and administration offices, which made the centre attractive, and today it has over 20 companies employing 600 people. The centre is a private company and not sponsored by either the public funds 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 organization 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. A start-up company is in this case a business that arises directly from R&D conducted at a university. The technology transfer services support new start-up companies the first year with infrastructure, advice, and financing. The services also include commercialization of research results that is protection of intellectual property (e.g. patents), and training and education for scientists. The collaboration is a benefit to both the universities and companies; the companies get access to top scientists for joint research, and for the scientists this creates a new job opportunity[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 an importance in applying its research in the industrial and public sector. In order to do this, the University of Basel has implanted its own Office of Technology Transfer (OTT). Its purpose is, as other technology transfer organizations, to evaluate the commercial use of research results, protect intellectual properties, and transfer the results to the public sector or to the industry. The University of Basel also supports start-up companies, in form of assistance by offering academic advice or working space, instruments, and assistance in establishing first contacts with business and venture capitalists for financial support[235].

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[233] Innovationcenter of North-West Switzerland, <http://www.innovationszentrum.ch/About.htm>
[234] Unitectra, <http://www.unitectra.ch/en/portrait/6.htm>
[235] Wissens-Und Technologie Transfer Uni Basel, <http://pages.unibas.ch/wtt/TT-Philosophy/tt-philosophy.html>

11.5 Comparison of the 4 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 factor conditions, such as financial support, skilled labour, infrastructure, and related and supporting industries, including collaboration between the companies and research communities[236]. The results from the case study suggest that a life science cluster requires a satisfactory science base with high-level research for its success. This is what differentiates the pharmaceutical industry from many other industries; it is a science-driven business, and therefore proximity to top universities is important. From this perspective, Massachusetts is leading, due to top-level research at world-class universities, such as Harvard and MIT. In addition to the science base in Boston-Cambridge the highly skilled workforce and daily interaction between industry and academia are important factor conditions attracting big pharma.

Indeed Massachusetts has the most R&D units of the clusters in this study, 22 big pharma R&D units. Switzerland has 11, Ireland has 8 and Singapore has 8 big pharma R&D units. Within this industry one of the main competitive advantages is to have access to and to build expertise in the biomedical sector. In this area, good is not enough, deficit 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 commercialization. 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 programs. One common advantage for all businesses in these clusters is the high concentration of pharmaceutical companies in the region, access to top-class laboratories, and the creation of networks, such as innovation centres that foster partnerships between academia and the industry.

Government policy is an important initiative in creating successful clusters[237]. A strong government leadership can help creating 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 foundation upon which companies contend in a region. These economic foundations provide availability of financial capital 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 €184 billion NDP plan 2007-2013, whence €6.1 billion of them will go to science, technology, and innovation, is central to the Irish goal of becoming a global knowledge based economy. SFI have big opportunities to build and strengthen scientific research and benefit to the long term competitiveness of Ireland. This in turn, can be an issue, since the economic development in Ireland is strongly government-led.

[236] Porter, 1990.
[237] Ibid.

Massachusetts has the highest levels of NIH funding per biopharmaceutical employee in the USA. The region received $2.27 billion in 2005, which makes it the most strongly government supported cluster, when comparing to Ireland, Switzerland, and Singapore. But the NIH funding has levelled off markedly since 1998, if the decline in funding continues, Massachusetts will lose this leadership. 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 provide an attractive location for their 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 €25 million, but is still far from the aggressive venture capital communities in Massachusetts and Switzerland. Singapore needs to develop the 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 for 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 will decrease the corporate tax rate from 20% to 18% in 2008. This places Singapore in the second place, after Irelands 12.5% corporate tax rate, if the Swiss canton Zug is excluded with its 17.8% corporate tax. The remainders of Swiss states overlie approximately 25%. For manufacturing operations, Ireland is the best location partly due to its previous *Manufacturing Rate of Corporation Tax* that was 10%, and remaining at 10% till 2010. It will increase to 12.5%, but still making Ireland the best location for manufacturing units tax-wise. This can be seen in our empirical data: Ireland has 40 manufacturing operations located in the country, while Switzerland has 20 manufacturing operations, Singapore has 14, and Massachusetts has 13 manufacturing units. Massachusetts has the highest corporate tax rate both in the nation and when comparing to the other clusters, but the *Single Sales Factor*, has significantly reduced the firms' state tax that leading up to Massachusetts becoming the most competitive state regarding state tax weight, especially for medium- and large sized companies, since the 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 light of the intense competition for top scientist, 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, mainly due to its unique proximity to world-class academic institutions, major teaching hospitals and well financed and aggressive venture capital community. Ireland is attracting multinational companies mainly due to its low corporate tax rates. Singapore also attracts foreign pharmaceutical companies and pharmaceutical start-ups because of its tax incentives, as well as its comprehensive air and local infrastructure that provide flow of goods and services to markets around the world. The company-friendly infrastructure increases the competitiveness of Switzerland. Furthermore, the Swiss taxes

[238] Ibid.

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 the economies have grown in Asia, 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 also in Singapore. After the establishment of manufacturing units, came clinical trials to use the potential of the enormous populations in China and India. This in turn was followed by location of R&D units to take advantage from the large group of highly skilled and educated scientists present.

The new localizations in Asia are not only dependent on the lower wages of the workforce, but also on other economical incentives such as lower taxes and subsidiaries. Furthermore, especially China and India are huge markets with a low degree of penetration, showing potential to become two of the most important future markets for pharmaceutical companies. However, localization 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 competition from generic drugs, both legitimate and illegitimate, is the issue with protection of intellectual property, which in many cases is either far behind the western laws or is not enforced properly. However, this problem has been recognized and both China and India are trying to put an effort into improving this. In this case Singapore, with stricter laws, is an interesting location.

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 following comparison of China and India.

12.1 China

The Chinese economy has been undergoing tremendous growth during the last decades, keeping an average annual growth of 9.8% between 1993 and 2005[240]. However, this magnificent growth has also brought on a titanic problem, the Chinese environment is severely damaged and the land and water is badly polluted. Also, the economic growth is not evenly spread within the country, the coastal parts are driving the growth while the inland is lagging behind in many aspects. The economy is growing, maybe even a little too much risking an overheating, and foreign investments are increasing. For foreign

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

[240] Deutsche Bank Research. 2005.;
'China lifts annual growth figures', 2006, <http://news.bbc.co.uk/2/hi/business/4594132.stm>

companies China has mostly been a manufacturing hub, mainly because of low wages and an abundant workforce.

This has been true for 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 in the highly educated Chinese workforce.

The Chinese healthcare market was worth about $35 billion 2004, and expected to grow rapidly to a value of around $350 billion 2025. This quick growth is fuelled by the growing Chinese middle class and the 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 both privately and 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 corporate tax in China is today 33%, however for foreign enterprises located in the coastal cities it 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. These taxes may however be subject to future change, since a discussion about a flat tax rate of 25% have been conducted. [243]

12.1.1 Strengths

Among the most important strengths of China is its population. The population provides the 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 USA when it comes to the number of R&D researchers, totalling over 800,000 in 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 a 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 modernization of traditional Chinese medicine.[245]

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[241] McKinsey & Company, <http://www.mckinseyquarterly.com/article_page.aspx?ar=1798&L2=7&L3=10>
[242] Capie, 2007, pp. 98–105.
[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.

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

China is currently far ahead of India in foreign direct investment, a lot of this is due to a more effective legislation regarding this. The government has changed the laws and policy from being restrictive allowing foreign investments only in approved joint ventures with domestic companies to allowing free foreign investments. [247] In 2004, China attracted over $60 billion in foreign direct investments[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 organization (WTO) in 1999, the Chinese laws have been updated to comply with WTO standards, which is an important corner stone in promoting commercialization of science and innovation, and for trade in general. However, as of today these laws are not enforced, making the laws 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 protection of intellectual property. [249]

The previously mentioned issue is linked to the low R&D spending in China, for example China spend 1.23% of GNP (2004) compared with the USA, Japan and Germany that spent more than twice that number. Furthermore, in a similar comparison publication in scientific or technical journals in China is 30-40 times lower per capita than that of the USA, Japan and Germany. As for the domestic Chinese pharmaceutical industry R&D spending is low, and innovation is low as well. 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 for savings accounts is lower than the inflation, meaning the Chinese people lending money to the banks are making a real loss. This has created a grey market for loans, with higher interest; the money from this business is then

[246] Ibid.
[247] Zeng & Wang, 2007.
[248] UNCTAD, 2005.
[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>

loaned to private companies at a high interest rate. To work in a more efficient way the "real" bank will need higher interest to attract the savings of the Chinese people, to be able to loan money to private enterprises. 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 before mentioned lack of protection intellectual protection, since to be able to provide return on investment in new ventures in high technology businesses, the innovation needs to be protected[253]. With a large uncertainty about the possibilities to get return on the venture capital investment, the market for providing venture capital becomes unattractive.

12.1.3 Opportunities

Chinas market is large and growing quickly, this is an important reason for companies to establish themselves in China. The growth in the pharmaceutical market is driven partly by the overall economic growth, but also by the quickly growing Chinese middle class with money to spend on healthcare. According to Qin et al. the economic growth, is also important since it is driving demand for investments in China[254].

Another opportunity for China to attract foreign direct investment is the lower tax for investments in certain economic development zones. These economic advantages may drive investments in these areas; however they may still change and not be an everlasting incentive to stay in China.

To stimulate investment not only in manufacturing operations, but also to larger extent in R&D operations harder enforcement of the implemented intellectual property protection laws are needed. It can be seen that since the laws were implemented, the investments by big pharmaceutical companies in R&D in China have risen according to this study, although the new laws are not the sole reason for this. The enforcements of these laws are not only for the foreign pharmaceutical companies, but also aids in creating a favourable environment for domestic research-intensive companies.[255]

Also to improve the economical environment for new innovative firms, a better availability of venture capital is needed. An important part in creating this is an improvement of the banking sector, to make the use of capital more efficiently.[256]

To increase the competence needed from the employees in a technology intensive industry a reformation of education system is needed. Compulsory schooling need to be improved and need to reach the rural areas as well and not only the coastal cities. Together with an improved tertiary education this can provide an even greater workforce for the pharmaceutical industry.

[252] Zeng & Wang, 2007.
[253] Maskus, Dougherty & Mertha, 1998.
[254] Qin, et al., 2006, pp. 751–774.
[255] Maskus, Dougherty & Mertha, 1998.
[256] Zeng & Wang, 2007.

12.1.4 Threats

The Chinese economy is showing a high inflation rate, far above the government goal of 3% - the actual rate was around 6.5% in November[257]. This has happened despite five recent interest rate raises by the Chinese central bank. An overheating of the economy may create excess demand for goods and thwarting investments in China. However, if China is overheating or not is something economists are disagreeing on.

A global competitive environment is bringing new challenges for China. As the wages in China are rising one comparative advantage is diminishing, creating possibilities for competitions from other countries with lower wages. Also India is rising up as a competitor to China with a huge workforce and which may also possess a higher competence. A risk here is the lack of domestic innovation in China, causing a dependence on foreign innovation.[258]

The Chinese society is becoming increasingly divided by the urban areas and the rural areas, for example in the levels of wages, education and foreign investments. This gap is threatening to destabilize the society and to decrease the growth over a longer term.[259]

A huge challenge for China is the destruction of the environment and the need for a changed attitude towards it. According to the World Watch Institute, 16 of the world 20 most polluted cities are in China and this situation is not likely to improve over the coming few years. This is partly due to the Chinese reliance on coal powered electrical plants. Furthermore, the rivers in China providing much of the fresh waters are heavily polluted as well, creating a shortage of clean water.

The huge generics market is a challenge not to China as a country, but to the foreign companies establishing themselves in China to try to gain market shares on the pharmaceutical market. To try to compete with this lower prices are needed, meaning lower margins.

12.2 India

Much alike China, India was industrialized in 1950's and was then an economy dominated by state-owned companies. India has not been able to keep up with the extraordinary Chinese growth, but still has sported great number averaging 6% of growth since 1980. This number has seen an increase during the 21st century, as the Indian economy has grown 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 sector. For example, a large number of companies have outsourced their call centres to India during the last decades. According to a study conducted by Deutsche Bank, it is concluded that domestic Indian companies are generally better

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

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

As in China, the development in India has gone from only housing manufacturing of multinational pharmaceutical firms, to also accommodating 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, a large focus has been laid on being in the forefront of the development of the first generic biopharmaceuticals[262].

India has several universities known across the world, graduating more than half a million student yearly in biotechnology, bioinformatics and biological sciences. The Indian scientist also has an advantage to the Chinese because of their higher level of English due to their colonial history. Even though India has high peaks in the level of education, it also faces some of the same problems as China with the education level being significantly lower in the rural areas.[263]

The barriers of entry on the Indian pharmaceutical market are relatively low. This has made the industry fragmented, and created many minor players and a higher cost competition. This may decrease with the recent introduction of new patent laws. Another aspect of the cost competition is the price regulation set up by the government. The prices of drugs are set by The NPPA (National Pharma Pricing Authority), which is lowering 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, relying on economic incentives, such as lower taxes or even no taxes for a limited period of time. The foreign investments in India has increased during the last decade, however China 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 costly as producing

[261] Deutsche Bank Research, 2005.
[262] A 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>
[265] Swedish Trade Council, New Delhi, 2005.
[263] *Entry Strategies for Foreign Investors*, <http://siadipp.nic.in/policy/entry.htm>; UNCTAD, 2005.

within the OECD and sometimes even less, providing a big cost advantage in price sensitive industries[266].

India currently has the largest group of English speaking scientist outside the USA. India has some very well respected universities and a huge amount of students in tertiary education. The Indian universities have created a large and 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 a large potential for improvement[267]. This large population, and still lower wages than in the west, makes it an interesting location to conduct clinical trials as well.

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 a bit to go before it reaches the same level as in many of the OECD countries.

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

12.2.2 Weaknesses

India is still far behind the west in the level of infrastructure. In the rural areas electricity and clean water may be scare commodities[269]. This is an issue since the company might have to build up this infrastructure themselves when establishing a new facility, decreasing the cost advantage of the location. Some of state-owned assets may need to be sold, and the money invested in infrastructural improvements to further stimulate growth[270].

The Indian labour laws are quite rigid and the trade unions are powerful. The laws were made when India was still a socialistic state with government owned factories. An example of the laws is that a company with more than 100 employees cannot fire them without approval from the government. This creates a rather rigid labour market. According to Kundra, this adds cost to production in India decreasing the cost advantage[271].[272]

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[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>
[270] Srinavasan, 2006.
[271] Kundra, 2003, <http://www.hinduonnet.com/thehindu/biz/2003/06/02/stories/2003060200100200.htm>
[272] Srinavasan, 2006.

12.2.3 Opportunities

Similarly to China, India has had weak protection of intellectual property. Previously a product could not be patented, what could be patented was the process. Meaning as long as a product could be produced in a slightly different way, the patent could be sidestepped. Today India has adapted intellectual property protection as stipulated by the World Trade Organization, and products as well can now (since 2005) be protected by patents.[273] This new protection of intellectual property, coupled with an increased effort to enforce the laws, can now provide even better growth possibilities. According to Gould and Gruben a strong protection of intellectual property is better for the economical growth[274]; furthermore the stronger protection can increase the margins for multinational companies and increase the focus on R&D for domestic players[275]. The domestic Indian companies have a more 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 becoming the world leader in biopharmaceutical generics[277]. Groundwork is being done, to provide an opportunity to start exploiting the first biopharmaceutical patents ending. This is, however, more challenging than regular generic production. If this investment is fortunate, it will give India a leading role in this future market. Biotechnological production lines are generally more complex than regular chemical production line, making the success more uncertain, but there is no doubt a great potential in this market.

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

To improve the scientific output in India large government funded R&D programmes have been initialised in India. These programmes are ambitious and set to triple R&D spending between 2004 and 2007, to reach 2% of GNP. The goal is to build up a strong knowledge-based economy. Today the R&D spending is low compared to OECD, but India is trying to catch up with the west and by introducing stronger intellectual property protection larger R&D investments are likely to be encouraged, both from domestic and international companies.[278]

12.2.4 Threats

The Indian economy is less integrated than the Chinese in the world economy. Reasons for this may be more restrictive laws for foreign investments and import of goods. This protectionism

[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] A Sandström, 2007, [Personal communication].
[278] Schoen, 2005.

could threaten the economic growth, linked to this are also the strict labour laws, which have the ability to scare foreign investors. [279]

Currently a threat of an HIV/AIDS epidemic is facing India; an epidemic which is having its worst effects in the most prosperous parts of India. This could prove to be 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 a percentage in India by 2019.[282]

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

12.3 Comparison of China and India

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

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 communistic single-party state. The Indian market is a market economy, although it is regulated, while the Chinese government is striving for a socialist market economy, where the state owned and private companies compete freely. The Indian market has government regulated pricing for pharmaceuticals and also 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 the government has a stronger influence.

China and India share many characteristics as fast growing economies and markets with huge populations. It is also these mentioned characteristics, which probably are the most important drivers for establishment in China or India. The population, contain large groups of highly educated and skilled professional, but also enormous inequalities in education and income, especially between urban and rural areas. An advantage for India in this aspect is the number of English speakers.

As they share advantages, they also share some problems, maybe the most important for the patent and research dependent pharmaceutical industry is the issue of protection of intellectual property. 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 for the pharmaceutical industry with

[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/>

counterfeit drugs. There is also a competition on the domestic market from cheaper generic drugs. Especially in India there is currently a big focus on producing generic biopharmaceutical drugs in the near future.

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

According to a report by A.T. Kearney China is today the most attractive location for clinical trials outside the USA, followed by an India in second place, with similar rankings over the categories, except advantage for China in relevant expertise and an advantage for India in regulatory conditions. Both China and India are showing a clear low cost advantage compared to the USA.[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 to a large extent satisfied by generic drugs, which are manufactured by local companies. However, as the middle class is growing an increase in sales of the regular, more expensive, pharmaceutical could be expected.

12.3.3 Related and supporting industries

China is currently in front of India when it comes to foreign direct investments, but the investments in India are increasing. When it comes to spurring domestic innovation in the pharmaceutical sector India is ahead, partly because of a higher availability of venture capital for new companies. Also the Chinese banking system is facing troubles, with bad loans, high inflation and inefficient use of capital. Generally the innovation in domestic enterprises, especially in China, is rather low in the pharmaceutical sector.

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 USA or Europe. With an increased education level and R&D presence this is somewhat changing to conducting more operations in China and India. The growing domestic market in both countries is changing the strategy somewhat, making companies also locate in China and India to gain access to these markets.

The source of advantage in the pharmaceutical industry is generally described as 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.

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

Currently a larger number of big pharma companies have operations in China, than in India. Of the ten largest big pharma all of them have a presence in both China and India. Moving down the list first the presence in India is decreased and thereafter also the presence 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 seen by these numbers, the relationship between manufacturing and R&D units is roughly the same in both countries, with manufacturing unit making up the majority of the 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. No doubt, there is a clear movement toward Asia and 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 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. Particularly there is disagreement whether big pharma *successfully has adjusted* its business facing this new industry landscape.[284] Furthermore there is disagreement on the exact *character* of such an adjustment.

Indeed we know from our empirical study that both research and manufacturing activities involve biotech applications. Furthermore there have been many accounts on 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 at least has reacted to the applications of biotechnology.

Whether or not these adjustments should be considered successful or not naturally lie in the specific criteria for a successful company being used. If success is measured solely in the numbers of pipelined pharmaceuticals concerns may be raised. However, some point to the fact that such measures do not truly capture the *innovativeness* of big pharma and that these firms indeed are successful (or at least not *less* successful than before)[285]. Others relate declining numbers of pharmaceuticals from in-house R&D as evidence for a change in the business concept of big pharma[286]. This change makes big pharma less vertically integrated and more specialized on contracting and marketing pharmaceuticals from the research leading biotech spin-offs.

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 in the increased reliance on findings within smaller biotech companies.

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

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 highly skilled workforce. The leading Asian countries are Singapore, China, and India. These countries allure multinational pharmaceutical companies by offering savings on R&D costs, low-taxes, grants, and infrastructure support. Some companies, like Schering-Plough choose Singapore as its manufacturing and R&D hub in Asia, mainly due to its comprised rule for the protection of intellectual property rights, while other companies 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 offer off-shoring opportunities across all phases of the innovation value chain and they all stake on new skills and resources do keep coming. Common weaknesses that India and China have are the intellectual property protection. This may hold back the degree of innovation and product development of multinational companies. This 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. Singapore has 33 manufacturing operations and 9 R&D units., even though the difference in size of the countries are enormous. The stakes are clear that companies in Asia are establishing themselves as manufacturing hubs.

13.2 Reflections

This paper has been dedicated to unravel, analyse and explain the geography of big pharma R&D and manufacturing activities. Naturally the explanations depend on the extent to which such a geography could be determined. As previously mentioned it has been difficult to get values for parameters such as workforce and investments from these corporations. Furthermore the number of discontinued plants reported has been low. Better information would have improved the analysis considerably, adding a size dimension to the units rather than just a number.

The analysis has been engaged in the quest of explaining the big pharma geography by drawing from 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 hand, every individual location is related to the state of the specific firm in question. Furthermore many units were located at a time when the pharmaceutical industry was different from what it is today.

13.3 Further Studies

A number of subjects suitable for further research have also been identified. Firstly, a study that focuses on the details of the units, i.e. accounts of size and specific operations, would be useful. However, to find these details there would be a need to successfully make

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

contact with important information sources within the companies or by using government statistical databases. According to our experience both of these information resources are problematic to use. However, this type of information should indeed be available to the companies themselves, but without any obvious gain for giving it out companies hold on to the information. Regarding 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 the big pharma geography is global, a lot of effort would be required to find some adequate way to harmonize such information.

In this master's thesis there have been accounts on the increased network structure of the pharmaceutical industry. Thus one relevant study would be to include the different 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 localization of smaller pharmaceutical companies and big pharma.

14 Conclusion

This master's thesis has been 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. 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 to reduce costs.

- The localizations 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 localization decisions seem to be driven to a lesser extent by historical factors and more by rational reasons.

- Analyzing the data collected in the empirical study, evidence of areas with high concentrations of big pharma activity can be found, so called clusters. These clusters have emerged from different backgrounds and developed into entities with different characteristics, such as focus on manufacturing or R&D. Not surprisingly the major pharmaceutical industry clusters are found in industrialized countries and often in connection to an extensive pool of knowledge and competence in the field. This is especially true for R&D operations.

- The big pharma geography of R&D units in Europe can to some extent be understood in the light of the character of technological change and the strategies of TNCs and Nation-States. More specifically, the revolution in molecular biology has had some impact on the big pharma geography especially in UK and France.

- Certain dynamics in the localization of big pharma can be observed, e.g. 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 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 import market for the pharmaceutical industry.

[288] NERA Economic Consulting. 2007.

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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 web sites, annual report or form 20F and form 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 Seiyaku
AstraZeneca	Takeda	Sankyo	Genzyme	King
Johnson&Johnson	Astellas	Otsuka	Serono	Tanabe Seiyaku
Merck	Schering-Plough	Forest Labs	Allergan	Kyowa Hakko
Wyeth	Bayer	Daiichi	Mitsubishi	Mylan Labs
Bristol-Myers Squibb	Schering AG	Baxter	Gilead Science	MedImmune
Eli Lilly	Genentech	Akzo Nobel	Lundbeck	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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