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Doing Good by Doing Well? The Political Economy of the Medical Biotechnology Industry in the United States

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DOING GOOD BY DOING WELL? THE POLITICAL ECONOMY OF THE MEDICAL BIOTECHNOLOGY INDUSTRY IN THE UNITED STATES

by

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Abstract

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This study is dedicated to the political economy of the medical biotechnology industry in the United States. The study combines interviews with more than 150 biotechnology actors with a historical analysis and evidence from publicly available data bases. The ascent of this new industry took place in the United States first and foremost, because there, scientific advancements coincided with the rise of supply-side economics, a policy shift that was part of a larger, neoliberal, ideological shift. Despite free-market rhetoric, specific clusters within the United States became the world's leading biotechnology clusters because of a history of targeted interventions to stimulate economic competitiveness. And despite much expectation about a 'biotechnology revolution', biotechnology became an outsourced sub-industry for research, embedded within the 'blockbuster drug' business model of large pharmaceutical companies. This business model benefited from America's healthcare system, whose fragmentation and domination by private health providers proved to be global drug companies' most profitable market. To keep the status quo, biotechnology and pharmaceutical industries have successfully engaged in political maneuvering. They have helped preventing or watering down U.S. healthcare reform efforts, not in the least the most recent ones under President Obama.

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Chapter 1: Biotechnology in Times of Neoliberal Ideology

1.1 Introduction and Summary of Findings

"*Biology is as important as the sciences of lifeless matter, and biotechnology will in the long run be more important than mechanical and chemical engineering*"

(Julian Huxley, The Retreat from Reason: Conway Memorial Lecture Delivered at Conway Hall, 1936)

"One egg, one embryo, one adult – normality. But a bokanovskified egg will bud, will proliferate, will divide. From eight to ninetysix buds, and every bud will grow into a perfectly formed embryo, and every embryo into a full-sized adult. Making ninety-six human beings grow where only one grew before. Progress."

(Aldous Huxley, Brave New World, 1932)

This study is dedicated to the political economy of the medical biotechnology industry in the United States. It analyzes the neoliberal conditions under which new biotechnologies have been invented and commercialized. Neoliberal doctrines and policies assume that human well-being can be achieved best by unleashing individual entrepreneurial freedom within the institutions of private property, free markets, and free trade, while the state withdraws from the provisions of public services. The genesis of the biotechnology industry coincided with the rise of these neoliberal premises. The specific way in which

neoliberalism unfolded in the United States has fostered a biotechnology industry that became embedded in an innovation model for medicines in which entrepreneurialism and optimizing returns on investment are central.

The subsequent study of the biotechnology industry is a critique of this neoliberal creed. Whereas the biotechnology industry is testimony to the successes of the liberated entrepreneurial spirits, it is also a valuable case in point about the inconsistencies and the side effects of neoliberal ideology put into practice. To begin with, it shows that laissez-faire never has been – never can be – without massive state intervention: It was thanks to a variety of different government support initiatives that the United State became host to the world's most sophisticated biotechnology industry. A side effect of this achievement is that this industry now contributes to the hefty premium for prescription drugs in the United States. These are undermining the sustainability of America's health care system. America is not only the country with the world's most expensive healthcare system, but it is also the only industrialized nation that does not have overarching governmental provisions for healthcare or price control in place. The centrality of America's fragmented, unregulated healthcare system that allows for exceptional premiums and profits is crucially acknowledged by the investment industry, which continues to warn about the specter of price controls in the U.S. prescription drug market. It has, however, not been addressed by previous studies of the biotechnology industry.

The following analysis is organized around three main contentions: First, it is not surprising *that* market forces and individual gain have driven biotechnological

advancements, but *how*. To begin with, biotechnology is a platform technology that is being used for a variety of purposes, such as plant breeding, waste water management, and the development of medicines. Yet the potential for profits is much bigger in human medicine than for any other applications of biotechnologies, and the scientific and economic impact is most relevant in this field. There the innovative activities of biotechnology firms and the ascent of a new industry illustrate capitalism's potential for creative destruction. So far biotechnological approaches to medicine and drug development have been captured by the 'blockbuster drug' approach, generating drugs for the industrialized world worth at least $1 billion in annual sales. Alternative attempts have repeatedly failed: For instance genomics, the science of the structure and the functioning of the genome, tries to capitalize on the variations in humans' genetic information, which could in theory lead to more tailor-made drugs. In practice, however, as this study will demonstrate, genomics did not lead to an overthrow or at least a disruption of the business model of large pharmaceutical companies. Rather, genomics became integrated into the development of blockbuster drugs. And despite biotechnology's posture as a new, nimble high-technology driven business that is clashing with the culture of sclerotic, innovation-poor, large transnational pharmaceutical companies ('Big Pharma'), the reality was a rather complex co-evolution. A new division of labor emerged in which biotechnology became a sub-industry for a global drug industry that went through its own technological and organizational transformations at the same time. Most importantly, the vast profits that Big Pharma's blockbuster drugs generated – thanks in large part due to ever-increasing sophistication and innovation in marketing – benefited a fledgling biotechnology industry.

Moreover, despite scientific discoveries having taken place earlier and elsewhere, this new industry took off in the United States in the late 1970s. At that time, nowhere else did scientific advancements dovetail with a number of political changes informed by a neoliberal ideology. Whereas neoliberal changes took root after the 1970s in many countries, the neoliberal turn in American society at large was most profound and so conducive to the ascent of the biotechnology industry that specific locations in the United States still remain unparalleled centers of biotechnological excellence up to this date. Particularly important were governmental interventions to promote entrepreneurialism to regain lost economic territory for the United States from other industrialized competitors.

Finally, focusing on the state of today's industry, my analysis of the biotechnology industry is also a critique of the consequences of neoliberal policies. I will argue that a generally overlooked condition for the flourishing of the biotechnology industry is the money that large pharmaceutical companies can invest in it thanks to a highly profitable blockbuster drug business model. Globally, this business model has become progressively more dependent on revenues accrued in the United States healthcare market. Yet America's healthcare system becomes increasingly scrutinized for being the world's most expensive while being neither inclusive nor qualitatively satisfying. This study will explain how the biotechnology industry has contributed to this condition, which has become politically increasingly contested.

The remainder of this first chapter will first present a number of puzzles that make the study of the biotechnology industry worthwhile (1.2). At the end of the section three claims

will be presented that will also be guiding the study and the chapters ahead. Section 1.3 will pose theoretical challenges and shortcomings that this study wishes to address. Biotechnology will first be placed within the historical context of changing capitalist formations. Second, the concept of 'Varieties of Capitalism' will be introduced as a guide for further inquiry into how and why the United States developed a comparative advantage for this new industry. Subsequently, two key terms will be defined: First, the notion of 'biotechnology' will be specified and some key distinctions of the biotechnology industry vis-à-vis other businesses be presented (1.4). Since this study highlights the importance of historical developments, both for the development of biotechnologies, as well as for healthcare, I will then briefly define the notion of 'path dependence' (1.5). The next section will be dedicated to the research design, as well as the materials and the methods that this study on the political economy of the biotechnology industry will deploy (1.6). The first chapter will be finished with an outlook on the study ahead (1.7).

1.2 Rationale for the Study

Looking at the biotechnology industry confronts us with several puzzles. In general it seems that medical biotechnology has been a 'revolution in waiting'. As the initial quotes indicate, speculations about biotechnology's blessings and banes began as early as the 1930s. But also more recently, biotechnology's achievements continue trailing the promises. For one, diseases that affect predominantly people outside the industrialized world are almost completely bypassed. But even in the wealthiest country in the world, the United States, biotechnology's impact on improving health has been limited. Later in this

study, I will discuss the mixed impact that biotechnology has made on speed, safety, and costs of drug development.

This leads to a second, related, conundrum: Human beings deviate from one another according to phenotypical, physiological, and genetic parameters. In theory, a science honing in on these differences – biotechnology – could lead to better, tailor-made products and services. This would have as a consequence smaller target groups and different marketing strategies from the blockbuster drug approach to sell as many similar drugs at the highest price possible to as many people as possible. In practice, this one-size-fits-all-approach of Big Pharma continues to dominate the drug business. Like in the days of Henry Ford, when "*a customer can have a car painted any color he wants so long as it is black*", any disease is curable so long as it is treated with a blockbuster drug.

Not only the automobile industry, but most other producing industries have long left the days of Ford. It is therefore all the more surprising that biotechnology, often hailed as innovative and economically as decisive as information technology, seems to be unable to undo standardized product development. Flexible and individualized applications have been at the core of the information technology (IT) revolution. By comparison, the biotechnology and pharmaceutical industry are still at the stage of the IT industry in the 1970s, when large mainframe corporations like IBM, Univac and Honeywell Bull dominated the field. Only later did individualized products, such as personal computers, Apple iTunes, or free-of-charge-services, such as Google's, become available. Although these companies have by no means challenged the capitalist for-profit approach to

technological innovation, the variety of insurgent business models also led to more variety of applications of new technologies and ultimately, a more spread-out trickling down of innovation. It therefore deserves further scrutiny as to why biotechnologies have not spurned new business models (be they service-based, or for smaller sub-populations) that are economically viable to compete with Big Pharma's one-size-fits-all blockbuster drugs. Towards this end, my study will pay specific attention to the development of genomics.

Another question to be answered is this: Why is it that, despite the increase of global interconnectedness, the global medical biotechnology industry remains heavily concentrated within few regional clusters in the United States? Economic globalization has led to a relocation of production facilities for material goods to low-cost countries. Theoretically, the production of knowledge could be shifted around the globe even more easily than the facilities needed for producing goods. And whereas outsourcing has gained momentum in sectors such as IT, it has happened on a much lower scale for biotechnology. For biotechnologies, the United States' leading position remains uncontested with regards to scientific output and patenting, and the number and size of biotechnology companies (see section 2.8 below).

It therefore deserves attention how in the United States the specific needs of biotechnology entrepreneurs to conduct their business are accommodated. To what extent has this concentration been the outcome of the free flow of market powers and how far has it been the result of government policies and political interventions? Looking at creative destruction in innovation does not mean that the market does it alone. On the contrary, a

political economy of the biotechnology industry has to analyze how the rhetoric of unfettered markets dovetailed with specific government interventions to create the United States' competitive innovation regime for biotechnology.

Also, most innovation theories are informed by the neoliberal economic assumption that the individuals' desire for profit is the most productive engine for innovation. As long as the supply side of technological advancement functions properly, a broader benefit for society as a whole will ensue. But who exactly profits, for example, from the fact that the world's most valuable and profitable biotechnology company, Amgen, is headquartered in California? The answer to this question is determined by the frame of reference. At times, Amgen's shares were worth twice the combined amount of all publicly traded biotechnology firms in Europe. On a macro-economic level, this is clearly a sign for the competitive advantage that the company and the United States enjoy. On the other hand, Amgen's drugs are sophisticated biotechnology-based pharmaceuticals that cost tens of thousands of dollars annually (see 2.10 below). Such high-premium drugs benefit Amgen's employees, the company's shareholders (who may live anywhere) and patients who have access to them. For most Americans these drugs are prohibitively expensive and would become available only when remunerated by their health insurance. Expensive medicines like Amgen's drugs covered by employment-based healthcare have put a strain on the budgets of health insurances, which are tempted to cut benefits elsewhere or raise their premiums. Since about two third of Americans are covered by health insurance through their employer, it is the latter who complain that skyrocketing health insurance costs have become a disadvantage for American corporations vis-à-vis their competitors in other

countries. In sum, there is more than one way to look at Amgen's successful biotechnology drug business. Previous studies on innovation and business practices have ignored that the United States' successful global leadership in biotechnology may have come at the expense of rising costs and inequality in healthcare.

Looking at innovation for healthcare from the receiving end – products and services for health – is a particular challenge for the neoliberal approach: Public needs should best be fulfilled by private entrepreneurial activities. Hence, private corporations should be positioned best to unleash the potential of these new techniques. But in the context of healthcare, the *leitmotiv* of neoliberalism, liberating individual entrepreneurial freedom is particularly problematic. Health is one of the most undisputable good for the individual person as well as for society as a whole. Like land, labor, and money, which Karl Polanyi called 'fictitious commodities', also health can never be produced with the intent to be primarily a commodity. The extent to which the provision of health services is seen as a public or a private task is a politically contested balance everywhere. In the United States, more than in any affluent, industrialized country, healthcare is predominantly left to market mechanisms. The debate about healthcare reform in the United States that erupted since the Presidential elections of 2008 is atypical. Specifically for the United States, the question therefore is not *why* has the commodification of health has had a mobilizing effect, but *why not earlier?*

Addressing the above issues, the following inquiry on the biotechnology industry will be organized around three claims:

1) Biotechnology has been co-opted by the pharmaceutical industry's blockbuster drug logic

Whereas biotechnology has made considerable inroads on other industries such as agriculture, its most dynamic and profitable applications relate to human health. The creative destruction unleashed by the biotechnology industry has not instigated a 'biotechnology revolution', for instance by making biomedical innovations more geared towards individuals. But instead, creative destruction unleashed by the biotechnology industry has been reigned in and paid for by Big Pharma's 'one size fits all' blockbuster drug business model. Highly profitable, large pharmaceutical companies are continuously forced to develop new drugs and products to keep up with investors' profit expectations. As they can no longer do so alone and inhouse, big pharmaceutical companies underwent much reorganization, as a consequence of which biotechnology has become a sub-industry in a new global architecture for drug development. The increasing complexity and variation in the organization of pharmaceutical companies' business has not made drug development either cheaper or faster. Yet the blockbuster drug model continues to prevail thanks to Big Pharma's marketing power.

2) Economic stimulus politics trumps free-market rhetoric

Despite the free-market rhetoric, biotechnology was not the result of unfettered market competition and capitalism's creative destruction. Instead, the industry came into being in the United States at a critical historical juncture in the late 1970s when scientific advancements coincided with the neoliberal promotion of supply-side economics.

Domestically, these policies reinforced the already existing clustering of scientific excellence and resulted in the concentration of the industry in specific regions in the United States. Internationally, federal policies created a competitive advantage for the supply-side of biotechnology and the development of the industry in the United States.

3) The absence of federal price controls in America's privatized healthcare provides a comparative advantage for the biotechnology industry in the United States

As the biotechnology industry matured and became fully embedded in the business logic of pharmaceutical companies, the unparalleled incentive structure and the revenues provide for by the fragmented United States healthcare system became a crucial competitive advantage. Healthcare in the United States has historically evolved as a market-based system in which a complicated mix of first public, and later public activities developed over time into a labyrinth of conflicting incentives. In absence of an overarching federal regulatory regime for the pricing of prescription drugs, the reimbursement incentives of the American healthcare market are unparalleled: In no other country in the world do citizens spend more on prescription drugs. While the origins of this healthcare setup predate the modern biotechnology and pharmaceutical industry, these actors continue to profit from this uniquely profitable environment. Consequently, they have also had a keen interest in keeping healthcare reform at bay and so far have successfully wielded their political influence towards that end.

1.3 Theoretical Challenges and Value Added

The ascent of the biotechnology industry occurred against organizational and ideological changes in the political economy of capitalist states after the 1970s. At that time the post-World War II regime of capital accumulation had reached an impasse. This capitalist formation, dubbed 'Fordism', encompassed a standardized mode of production, exemplified by the division of labor at the assembly line, as well as a rather homogeneous mode of reproduction of labor. To overcome the crisis in capital accumulation, corporations resorted to a decentralization of production and diversification of consumption patterns. A more flexible, 'Post-Fordist' regime of accumulation ensued, and, promoted by the global ascent of Japanese corporations, at times dubbed 'Toyotism' (Hirsch and Roth 1986). Throughout the 1980s new production tools such as just-in-time-production and flexible supply-chain management were introduced that allowed corporations to respond quickly to ever-increasing changes in consumers' tastes. Such restructuring of corporations coincided with the ascent of neoliberal ideologies. As it was the case for corporate transformations from 'Fordism' to 'Toyotism', also neoliberal politics was a reaction to the declining profitability of traditional industries of mass-production and the crisis of Keynesian, demand-driven policies in many advanced capitalist countries.

Against this backdrop, the biotechnology industry provides insights into the functioning of capitalism's contemporary flexible, knowledge-based, modes of production on at least four accounts. First, biotechnology demonstrates the pivotal role that technological and organizational innovation play for capitalism. Capitalism's dynamism is the result of the innovative competition, which ties together winners and losers in a 'perennial gale of

creative destruction' (Schumpeter 1942). Second, biotechnology is a contemporary example for how capitalism extends proprietary relationships over previously uncommodified matters and activities. For example, without biotechnologies, genetic information such as that encoded in the human genome, could not have become a tradable good for drug development. Third, within the biotechnology industry a plethora of complex ownership and corporate governance structures can be studied that are representative for contemporary knowledge-based industries. With increasingly complicated models of financing and ownership, traditional capital providers, venture capitalists, shareholders, investment funds, patent holders, and corporate managers (who may be both a shareholder and a paid employee of a company) all compete for controlling a company. And fourth, despite the neoliberal rhetoric of unfettered markets, these market forces continue to rely on the regulatory power of the state. Advanced modes of production and capital accumulation make necessary an even more sophisticated state. Only an elaborate state apparatus can safeguard complex market operations such those financed by venture capital, or enforce new modes of ownership, for instance of intellectual property.

Therefore, while biotechnology reveals the innovative potential and the momentum of capitalism's creative destruction (claim 1), this alone would not answer the question why and how the United States became the country with the most competitive biotechnology industry. Obviously, the specific role and the patterns of support for the industry have to be analyzed (claim 2). To investigate the comparative advantage that biotechnology in the United States continues to enjoy, I will follow an approach to look at 'varieties of capitalism' (VOC) introduced by Hall and Soskice (2001). According to this theoretical

framework, much of the work that firms carry out is relational to alleviate coordination problems and to mitigate transaction costs, both within and outside the firm. Different capitalist nations have different comparative advantages depending on how coordination is supported by the country's institutions of political economy. VOC distinguishes between capitalist economies based on the way in which economic actors coordinate their endeavors and what kind of support a country's institutions of political economy provide for. On the one hand, there are liberal market economies (LME) such as the United States, in which formalized contractual agreements, hierarchies, and competition in the marketplace are the most important means of coordination among economic actors. By contrast, in so-called coordinated market economies (CMEs), such as Germany, Sweden, or Japan, informal cooperation, deliberation, and sanctioning is more important for coordination among actors. VOC assumes that the different capitalist types have institutional features and support structures that render certain types of industries and innovations a comparative advantage. This approach postulates that CMEs dominate in sectors where staff and financiers' longer-term commitment allows for incremental improvements of production systems. Conversely, LMEs should have a comparative advantage in certain technological sectors, such as semiconductors, software development, and biotechnology, where flexibility and speed are pivotal for rapid wholesale innovation (Hall and Soskice 2001, p. 39). Surprisingly, this assumption has never been investigated specifically for biotechnology in the United States, a gap that this study will fill. Taking the individual business actors of the biotechnology industry as the starting point, I will analyze in how far the institutional features mentioned above are indeed the most important for coordinating businesses of the biotechnology industry.

Yet up to this point, my analysis of biotechnology as a neoliberal industry would still be bogged down by the neoliberal mindset of supply-side economics. VOC, as well as many other macro-economically informed approaches (see chapter 3) tend to look at innovation predominantly from the supply side. Whether or not there is a demand for these innovations, or at whose expenses they are met, is regularly ignored when looking merely at the supply-side of the economy. This study therefore explicitly analyzes the unique role that America's fragmented, market-based healthcare system plays. It is, in international comparison, a key institution of political economy in support of the biotechnology industry in the United States (claim 3).

1.4 Biotechnology: What's in a Word?

'Biotechnology' is a term collectively used for very different techniques. Some of them, such as beer brewing and fermentation, were established throughout the ages of human history. Others, such as genetic engineering – the identification, splicing, and transferring of genes from one organism to another – were developed only at the end of the 20th century. For the purpose of this study I will adhere to the definition of the term most commonly applied, which was formulated by the Organization of Economic Cooperation and Development (OECD). It includes both the traditional and the most advanced applications and describes biotechnology as

> *"the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services"* (Bull, Holt, and Lilly 1982, Appendix I, p. 67).

This general definition entails various scientific disciplines, such as molecular biology, microbiology, cell biology, biochemistry, but also process engineering, and information technologies. As this study will focus on medical biotechnology, it means that these scientific and engineering principles, including the understanding and the alteration of the genetic makeup, are ultimately applied to improve human health. Thus, medical biotechnologies comprise the development and production of drugs, diagnostic goods and services, but also animated and non-animated tissues and fluids that fulfill bodily functions. Bearing in mind this specification, for reasons of convenience I will use the notion 'biotechnology' synonymously with 'medical biotechnology' unless stated otherwise.

Throughout this study, it will become apparent that biotechnology has become affiliated with different meanings not only scientifically, but also for commerce, for regulatory agencies, as well as for the promoters and for the opponents of these technologies. This may appear to be a technical argument, but it is also political. Several studies have highlighted the relevance of discursive strategies for the creation of biotechnological knowledge and the struggle to define the field (Bud 1993; Gottweis 1998; Kay 2000). Although these works have at times been too much focused on the power of the discursive processes alone, it would be equally wrong to ignore completely the power of controlling narratives. Throughout this study, language will be highlighted when it is used as a strategic asset. We will come across catchy phrases or promises: From researchers arguing

for the increase of public research funding as well as entrepreneurs and private companies that praise their products in the marketplace[1].

A case in point is that biotechnologies have generated various waves of enthusiasms. Almost predictably, there has been a new 'biotech hype' every 5 to 10 years: During the late 1970s, the first production of insulin and interferon promised cures for key diseases such as diabetes and cancer. After these prospects did not materialize, the next wave of enthusiasm arose in the 1980s around the possibilities of gene therapy. After a number of publicized failures with lethal outcome, the burst of this bubble in the mid to late 1990s coincided with the advent of yet another one: The sequencing of the entire human DNA and the promises this new science –genomics - made for curing diseases. As none of these scientific advances has lived up to its promises, it remains to be seen whether the currently most promising technology - stem cell research – can buck that trend.

The point is not that these new technologies did not deliver anything: Today, the production of human insulin by genetically modified organisms is well-established and has millions of benefactors. Also genomics has become a wide-spread tool in the discovery process for new drugs. However, the question that this study will answer is to what extent

[1] For example, Robert Bud (1998) describes how the investment house E.F. Hutton had taken out a copyright on the word 'biotechnology' as the title of a newsletter for investors in 1979. The publication dealt with the new, molecular biotechnologies and to separate them as new investment opportunities from earlier, more mature technologies, such as in fermenting. Shortly thereafter, when the first new biotechnology companies that were specialized on molecular biology launched their shares on the stock market, this brand new (or newly branded) industry promised an unprecedented rise in value than any other stock in the history of the New York capital market.

such ‘irrationally exuberant’ expectations are systemic to the overall functioning of the biotechnology industry.

In that vein, a political economy of the biotechnology industry has to acknowledge first, that this is an industry distinct from other businesses on at least three accounts:

First, the educational requirements to enter the field are particularly high. The knowledge and training that an individual requires to engage in biotechnology need a steep upfront investment with regards to training and academic resources. This is for instance different from the IT industry, where legions of teenage computer nerds are engaged in writing and improving computer software. Twenty-something old university dropouts have repeatedly revolutionized the industry by establishing IT empires such as Apple, Microsoft, and Google. The same is not true for actors in the biotechnology industry. The scientific background that is needed before one can successfully master and commercialize life sciences has to be earned the hard way, which almost inevitably implies several academic degrees and many years of bench top drudgery in a laboratory.

Second, and related, biotechnology is highly dependent on basic research, which has had particular consequences for the institutional setting. Whereas industrial research laboratories were at the basis of many science-based technologies, biotechnology was characterized from the beginning by its tight connection between academic research and industrial commercialization, which Kenney (1986) therefore called the ‘university-industrial complex’.

Third, biotechnology deals with animated substances, which, scientific advancements notwithstanding, continue to behave in unpredictable, non-linear ways. The testing on human beings of a new biomedical invention, for example, is not a mathematical problem whose outcome could be calculated a priori. Dealing with living organisms in general bears a high level of social controversy and uncertainty. From the beginning on, safety considerations as well as ethical boundaries regarding the manipulation of living material have added to this insecurity and political charge. What is technologically feasible - such as the manipulation of the genetic make-up of organisms - may not always coincide with what is tolerable within or across societies.

These aspects make biotechnologies much distinguishable from other advanced technologies[2]. These differences will have to be kept in mind, when the generation and commercialization of biotechnological innovations will be analyzed in the context of the United States in chapter 5.

[2] Breschi (2000) therefore speaks of technology-specific innovation regimes that comprise regulatory procedures, the scientific background involved, and the markets for disseminating the new technologies.

1.5 History Matters, But How?

Whereas everybody agrees *that* history matters, social scientists have come up with different concepts of *how*: Three of them – accidents, path dependence, and critical junctures - are presented here that will be relevant for my analysis of the biotechnology industry:

Accidents: Economists, who have acknowledged that the invisible hand of the market does not automatically lead to a unique single best solution, have called upon path dependence to explain how and why the outcome of market competition often depends on historical accidents. For instance, functional yet sub-optimal technologies continue to survive, because the costs to leave that path are getting increasingly higher the longer one proceeds on it. This phenomenon, in reference to the illogical keyboard composition of typewriters and computers is dubbed "*The economics of QWERTY*" (David 1985). Looking at the history of the biotechnology industry, for instance, it may or may not have been an accident that the techniques to recombine DNA were first discovered by Stanley Cohen at Stanford University and Herbert Boyer from the University of San Francisco, CA. It was not an accident, however, that these universities were more entrepreneurial than academic institutions in other countries. The combination of scientific and entrepreneurial prowess was the result of a history of encouraging policies. They sparked the first wave of biotechnology firms being spun off of academia in the U.S. – and not elsewhere. In other words, an analysis of the biotechnology industry must go beyond historical accidents,

because accidents only become consequential when they receive a longer-lasting institutional support.

Path dependence: In political science, the notion of path dependence reaches back to Theodor Lowi's dictum of *"policies determine politics"* (1972, p. 299). Such feedback loops between policies and politics shape subsequent political dynamics that get locked in a particular path of policy development that becomes increasingly difficult to reverse (Pierson 1993, p. 606). In path-dependent social processes, timing is of the essence: Early decisions are far more consequential than later ones for the ultimate outcome. And existing institutions and configurations are not necessarily a reflection of the status quo, but are often a sign of institutional inertia (Pierson 2000a, 2000b). Nevertheless, path dependent processes should be seen as dynamic: They are not defined by the absence of change, but by change that is

> "*channeled by the self-reinforcing mechanisms that propel the existing path of development."* (Hacker, 2002, p. 54)

The United States healthcare system is emblematic for this path dependence. As will be elaborated in Chapter 6, the early-on decision to organize healthcare provision predominantly by private actors, determined structural bias against public medical services that reverberated ever since ever since and stymied also the healthcare reform efforts of President Obama in 2010.

Critical Junctures: These are conceived as periods of significant change, which may – or may not – occur differently in different countries, and which are considered to generate distinct historical legacies (Collier and Collier 1991, p. 27). In the course of this study I will demonstrate that a 'critical juncture' occurred in the United States after the election of Ronald Reagan in 1980, which caused a turn towards neoliberal policies and ideologies. The ensuing shift towards entrepreneurialism and economic competition had two path-dependent ramifications for the biotechnology innovation regime: Domestically, these neoliberal supply-side economic policies profited biotechnology development most in those regions in the United States that, due to a number of federal policies, had already developed a crucial mass of scientific excellence. Internationally, they generated a critical competitive advantage for the biotechnology industry in these regions and a first-mover-advantage that other regions – domestically and internationally – have found hard to catch up with ever since.

In sum, the history of policies in favor of the supply-side driven scientific development and market-led solutions for public problems has generated a momentum on its own. As the difficulties to reform healthcare in the United States demonstrate, they led to entitlements and entrenched political positions. A case in point will be presented in Chapter 6, which discusses the joint influence that biotechnology and pharmaceutical industry have wielded to bend any proposal on healthcare reform according to their needs.

1.6 Research Design to Study the Political Economy of the Biotechnology Industry

The neoliberal conditions under which biotechnologies have been invented and commercialized can best be analyzed from the viewpoint of the individual entrepreneurial actor. Ultimately, it is s/he who – motivated by the pursuit of private gains – should set in motion innovative entrepreneurial activities to the larger benefit. This first step of my investigations is inspired by the approach to study 'varieties of capitalism' of Hall and Soskice (2001). VoC postulates that LMEs should be particularly advantageous for fast-paced innovative technologies such as biotechnology. In compliance with predictions made by VoC theory, the U.S. is host to the world's by far largest and most competitive biotechnology industry[3]. This study is a critical review of the assumptions why and how the United States institutional support structure is advantageous for generating and sustaining the most competitive biotechnology industry. Based on interviews with biotechnology entrepreneurs in the United States, this study analyzes the repertoire of companies' coordinating mechanisms and how these affect their strategic choices. Chapter 4 will present a detailed account of how biotechnology companies strategize in their decision-making, and on what kind of support institutions – formal and informal – this is based. Strategic decisions are for example, questions about what markets are entered, what collaborations sought, and where a company should be located. Not all the support structures mentioned are those highlighted by the VoC: Interviews will reveal the importance of, *inter alia*, patenting, access to scientific research, academic research staff,

[3] The data to prove this claim will be discussed in detail in Chapter 2.

and funding. Equally important will be to distinguish between the role of formalized versus informal coordination.

In a second step, therefore, by analyzing the individual firm acting within an institutional structure, the most important institutional support systems for the biotechnology industry in the United States are being identified. I will demonstrate how those most relevant are the result of federal policies. Many of them preceded the ascent of biotechnological innovation. Taking path dependence seriously, I will reconstruct the politics and history of a number of these institutions and support mechanisms. I will show how certain policies have lead to a domestic clustering of biotechnology, and an international competitive advantage. Whereas chapter 4 and 5 will be dedicated to the supply-side of technological development, this study in addition argues that the fragmented and privatized nature of America's healthcare system presents another important support structure for the biotechnology industry in the United States. The history and the political struggles around this setup will therefore be dealt with in depth separately in chapter 6.

For the gathering of information a triangulation strategy is employed that includes personal interviews, statistical data, and historical reconstruction through literature. While all these approaches will be helpful throughout the entire investigation, they will be given different weight for each individual claim. To obtain a broad and representative overview of firms' business strategies, its coordination mechanisms, and the institutional support, I conducted interviews in person and between October 2001 and October 2008. Interviews took place with senior level management representatives of 145 biotechnology companies located in

the United States. Interviews took between 45 to 60 minutes and were guided by a questionnaire (see Appendix). Similar to the ‘varieties of capitalism’ approach, the questions targeted firms’ strategic behavior with regards to key aspects of their decision-making and the support structures that they entailed. Issues inquired were for instance related to vocational training and education (to make sure to obtain – and keep – the proper workforce); corporate governance (to attract various sources of funding and manage the finances for the activities of the firm accordingly); and finally, internal coordination (to have employees act in the interest of the corporation, particularly with regards to information sharing). Moreover, it was tested whether these were indeed the most relevant aspects in companies’ decision-making process. Towards that end, additional closed, quantitative questions were asked (e.g. about company history and financing, number of co-operations, human resources), as well as open, qualitative questions (e.g. about R&D strategies, reasons for location, the utility of state and national support programs).

Understanding the different business strategies of biotechnology corporations is essential to substantiate all three claims of this study. A representative sample of biotechnology enterprises was surveyed to obtain a realistic depiction of the variety across the entire biotechnology industry. Firms included in the sample varied according to four main variables: Their location; the institutional support structures in these locations; companies’ different products and services; and companies’ developmental and ownership stage.

Location and institutional support systems

Location is a key strategic dimension for corporations' decision-making. Sampled companies were located in five distinct regions: Boston, San Francisco, Washington D.C., New York, and San Diego. All of these locations belong to the leading biotechnology innovation clusters in the United States with regards to the size and number of companies (Cortright and Mayer 2002). Moreover, despite the free-market rhetoric, biotechnology actors in those regions also enjoy comparatively more economic support than elsewhere with regards to federal research monies they receive (Battelle 2008). These regions' competitive advantages were the result of a long history of purposeful governmental interventions (see chapter 5). Comparing business strategies in these five locations offers variations in factors for competitive advantage, so that they can be weighed and put into chronological order. For example, if competitive advantage was only a matter of scientific excellence, one should assume that Boston should lead, because the region has the densest population of institutions of higher education, including Harvard University as the country's oldest and wealthiest elite academic institution. Yet today, the world's by far largest agglomeration of biotechnology companies is located in California. There, one hot spot continues to be San Francisco, where biotechnology as a business started in earnest when the first commercial entities were spun off from university settings. Another Californian cluster is located in San Diego, which hosts the fastest growing biotechnology agglomeration in the United States.

According to the VoC approach, the United States as a liberal market economy is supposed to be rich in formalized, hierarchical, contractual relationships. Towards this end, this study

will scrutinize the different institutional support structures in place. But it will also address the sub-national differences. For instance, California's well-established venture capital (VC) industry will be scrutinized as a comparative institutional advantage vis-à-vis other regions, such as Massachusetts. On the other hand, and contrary to the predictions of the VoC framework for liberal market economies, the relevance of non-formalized coordination for biotechnology actors will be scrutinized, too. Biotechnology seems to be flourishing best, where there is a chance for disseminating new knowledge also in a 'tacit' way (Audretsch and Feldman 1996). Seen this way, California's lead in biotechnology would be less a result of contractual agreements, but of a particularly entrepreneurial climate. Such informal factors have been considered to have given the West Coast a competitive edge over the Boston area with regards to information technology (Saxenian 1994).

Other locations offer insight into other institutional support structures: The inclusion of the Washington D.C. biotechnology cluster adds information about proximity to the federal regulatory bodies and the grant-making institutions, particularly the National Institutions of Health (NIH). The New York City conurbation, by contrast, is characterized by the major presence of two other institutional supporters relevant for the biotechnology industry: Located on different sides of the Hudson River are the world's largest pharmaceutical companies and the world's largest financial institutions. Last but not least, after the end of the Cold War the San Diego region has become the country's fastest growing biotechnology cluster. The city has a long history as a military hub and center of excellence for arms technology development. The longevity of these federal, state, and local

institutional support structures will have to be taken into consideration when looking at the conversion from one advanced technology to another.

Companies' different Products, Services, and State of Development

Comparing and contrasting a variety of companies' strategic choices helps understanding how capitalism's creative destruction runs its course among biotechnology firms and whether this industry is dominated by the economic and organizational imperative of the drug development logic (claim 1). Therefore, after choosing the different locations, the companies to be included in the survey were selected to reflect the variety of businesses present in the five regions. Towards this end, the membership directories of the following biotechnology associations were used: Northern California Life Science Association BayBio (San Francisco); Biocom (San Diego); Massachusetts Biotechnology Council (Boston); MDBio (Maryland); New York Biotechnology Association (New York). These industry organizations categorize their members differently. To apply a coherent set of characteristics throughout the survey all five clusters, I used the classification of the Biotechnology Industry Organization (BIO), the overarching United States biotechnology trade group. BIO distinguishes companies as follows:

1) Drug discovery/biomedical research: Companies carry out research, either for drug development or other biomedical purposes. This category includes also firms engaged in genomics, the science of the sequence and functions of genes.
2) Diagnostics: Companies develop biotechnology-based diagnostic tools that measure bodily functions on the physiological level (e.g. glucose) or pathogens (e.g. HIV).

3) Biomedical devices: companies develop a range of goods (e.g. artificial heart valves, drug-coated stents, and dialysis-related products) that combine biotechnology with mechanical engineering.
4) Contract research/services: Fee-for-service companies that deliver a broad range of products and services (biological reagents, testing animals, clinical trials).
5) Pharmaceuticals: Chemistry-dominated companies that develop, produce, and market drugs.
6) Environment and agriculture: Companies that provide biotechnology products for environmental (e.g. enzymes) and agricultural purposes (e.g. seeds).

In addition, companies selected were of different ages and stages of their development, and reflected different ownership models: Some were owned by private individuals, whereas others were publicly traded on the stock market. In both cases, some companies were independent, whereas others were subsidiaries of American or international entities.

Other Sources

In addition to corporate biotechnology executives, other relevant actors engaged in biotechnological innovation were interviewed, too. Two researchers in academia were asked to address the institutional changes and the various settings in which ‘basic’ and ‘for profit’ research commingles today. For the commercialization of academic research, universities’ technology transfer offices have come to play a pivotal role. Interviews were therefore conducted with technology transfer offices of three academic research institutions. In each of the five biotechnology clusters, a representative from the regional

biotechnology lobby group was interviewed. Finally, interviews have also been conducted with two institutional investors and two representatives from the venture capital industry.

Taken together, these interviews will illuminate relevant differences about how actors engaged in biotechnological innovation make strategic business decisions and what institutional support structures are most beneficial for that purpose. Interviews will elucidate to what extent companies engage in certain sets of biotechnological applications (pharmaceutical research) rather than other (such as environmental biotechnology, genetic engineering of crops, or genetic data sequencing), because of profitability considerations (claim 1). The interviews also illustrate the institutionally advantageous requirements for a company to conduct its business with regards to human resources, scientific infrastructure, access to financial means, markets, and how these factors affect their decisions on a location. Similarly, the interviews point out the role of state and federal support mechanisms, institutional and otherwise, that have turned out to be instrumental for the promotion of the biotechnology industry (claim 2). Information derived from interviews will then be contrasted with a historical reconstruction of science and technology policies relevant for biotechnology from the existing literature. Special attention will be paid to intellectual property and to understand how the industry's innovations involved increasing levels of commodification of the knowledge production process.

The repertoire of institutional support mechanisms brought to the fore by interviews will be complemented with official statistics and data about historic and current support and funding from public sources. A comprehensive compilation of state initiatives to promote

biotechnology is regularly provided by the Biotechnology Industry Organization[4]. Current figures for federal expenditures on R&D are made available by the American Association for the Advancement of Science (AAAS)[5] and budget allocations for biomedical research are compiled by the NIH Office of Budget[6]. Other relevant information about biotechnological innovation that will be used is made publicly available by the National Venture Capitalist Association (NVCA) and the Association of University Technology Transfer Managers (AUTM).

Interviewees were also asked about the importance for the biotechnology industry of America's fragmented healthcare market without governmental oversight of prices for prescription drugs (claim 3). To put healthcare in the United States in international perspective, interviews will be combined with other sources of information. Key health data from industrialized countries as provided by the Organization for Economic Cooperation and Development (OECD) will be compared. Subsequently, the current condition of U.S. healthcare is put into historical perspective by reviewing the history of United States healthcare based on fragmentation and market mechanisms. I will also study the interest group representation of the biotechnology and pharmaceutical industries with regards to preventing healthcare reform and drug price regulation. This part of the analysis is based on documents released by BIO, as well as the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents the country's leading pharmaceutical research and biotechnology companies.

[4] For the most recent update see (Battelle 2008).
[5] See http://www.aaas.org
[6] See http://officeofbudget.od.nih.gov/UI/HomePage.htm

Lastly, industry efforts to influence politics favorable to their strategic business interests are investigated. Relevant information is made available by organizations such as the Center for Responsive Politics that trace electoral campaign financing[7].

1.7 The Book Ahead

Chapter 2 will present basic information about how an evolving biotechnology industry became co-opted by the pharmaceutical industry (claim 1). A history of the pharmaceutical industry and how it re-invented itself several times provides the background to understand why biotechnology did not lead to a 'biotechnology revolution'. Contemporary data will be presented to demonstrate that biotechnology became sucked into the vortex of transformations of the global pharmaceutical industry whose center of gravity increasingly shifted to the United States.

Chapter 3 will explore the different theoretical approaches and methodologies chosen so far to analyze the biotechnology industry. Many of them do not offer insight into the relationship between the supply and the demand side for technologies, which would then also address questions of economic power and politics. My own theoretical framework tries to overcome such shortcomings of neoliberal supply-side theorizing. I will therefore first touch upon neoliberalism as a theoretical and political concept.

[7]See See http://www.opensecrets.org/

Subsequently, the possibilities and shortcomings of the VoC approach for the analysis of biotechnological innovation will be contrasted with ideas of creative destruction and the embeddedness of economic activities. Based on this framework, the subsequent chapters will investigate three claims mentioned above. Chapter 4 is dedicated to the findings derived from the interviews with biotechnology actors. Their decisions and strategies reflect how capitalism's creative destruction works in today's biotechnology industry. Also emerging from these interviews are a number of institutions and procedures whose support have become crucial for the strategic decisions that biotechnology managers take.

Chapter 5 will therefore sketch the history and politics of these institutions and the crucial role that the support of United States' government for the supply-side of technological developments has played (claim 2). I will describe how, after 1980, as a flip side of neoliberal free-market rhetoric, an array of federal policies to promote the biotechnology industry has been implemented. Historically these factors established the United States and specific regions as hosts of the world's most competitive biotechnology industry. Yet over time, as the industry matured, supply-side support for biotechnology innovation became less of a decisive factor. Instead, as Chapter 6 will elaborate, the politics and policies of America's deregulated healthcare system have become crucial for to the biotechnology industry (claim 3). I first provide a comparison of key healthcare data that demonstrate the outlier status of the United States healthcare system vis-à-vis other industrialized countries. Subsequently, a brief historic overview of America's fragmented healthcare system will be give, which provides the basis for understanding the difficulties of comprehensive

healthcare reform. Lastly, the chapter will address the lobbying efforts of pharmaceutical and biotechnology industries to keep healthcare reform and prescription drug price caps at bay. Chapter 7 will first summarize the findings of the study as they relate to the three claims. Subsequently, a number of intended and unintended consequences of the neoliberal policy prescriptions that shaped the biotechnology industry will be addressed. The resilience of the blockbuster drug regime will be questioned in light of the accessibility of increasingly expensive drugs. Other ramifications of the current innovation regime, particularly with regards to the production and commercialization of knowledge will be addressed too, as they have repercussions that go beyond the United States. Some concluding remarks are then dedicated to the future of the current biotechnology innovation regime as it will be affected by the current political and ideological tide towards a bigger role for government intervention.

Chapter 2: The Co-Evolution of Pharmaceutical and Biotechnology Industry

> *"The victories…over cancer, syphilis and tuberculosis will be as much capitalist achievements as motorcars or pipe lines or Bessemer steel have been. In the case of medicine, there is a capitalist profession behind the methods, capitalist both because to a large extent it works in a business spirit and because it is an emulsion of the industrial and commercial bourgeoisie."* (Joseph Schumpeter, Capitalism, Socialism, and Democracy, 1942)

2.1 Introduction

To understand the co-evolution of the biotechnology and the pharmaceutical industry, it is first necessary to recapitulate how the research and manufacturing of drugs developed over time. Throughout its history, the drug industry re-invented itself several times and whereas most of the key features of this business have changed, some have not. They will be addressed first in this introductory section because they provide the relevant background for addressing claim 1: To understand why and how the ascent of biological sciences, and the commercialization by biotechnology-startup companies did not lead to a 'biotechnology revolution', but became co-opted by a transforming, highly profitable, pharmaceutical industry. This transformation will be discussed according to three major epochs (Pisano 2002): A 'pre-R&D' period that lasted from the first records of human history until approximately 1945 (2.2) ; A 'Golden Age' of large-scale pharmaceutical R&D that lasted from 1950 to 1990 (2.3); And an 'Age of Transformations' ever since, in which the search

for new drugs had to keep up with ever-increasing profit expectations (2.4). Only during this last period did the biotechnology industry come into the picture. In this period of trial and error for new business models, the organizational changes of the pharmaceutical industry occurred increasingly to capture the scientific potential of the budding biotechnology industry (2.5). A real systemic challenge arose in the course of the late 1990s with the ascent of genomics, the science of the human genome. While this contender to the blockbuster drug model ultimately was muted (2.6), biotechnology was there to stay. One of the consequences was the shifting geography in drug development and commercialization (2.7), which led to the global pharmaceutical industry of today. Pharmaceutical companies eye the United States as the most crucial market, in which all the globally dominant players vie for market shares of multi-billion dollar blockbuster drugs sales (2.8). The global dominance of the United States is even more pronounced with regards to the biotechnology industry, as a number of scientific and commercial indicators illustrate (2.9). Consequently, today's drug business is characterized by Big Pharma embracing biological drugs, so-called 'biologics', some of which have turned into blockbuster drugs in their own respect (2.10). Yet as the conclusion argues, the commercial successes of a handful of biotechnology companies and their biologics pose no alternative, but rather corroborate the blockbuster drug logic: Selling drugs to as many as possible at the highest price achievable (2.11).

Ever since medicinal substances reached a level of industrial production there have been two distinct features that separate the commercial logic of the pharmaceutical industry from other industries: First, unlike for manufacturing businesses, the fixed costs for R&D are

high, whereas the variable costs for production are low. In other words, the cost structure is dominated by upfront investment in R&D that can only be recuperated later. Once a product (drug) is developed and approved, production costs, for example for another unit of the product, are not a decisive factor for competitiveness. The cost-cutting advantages of just-in-time production that have been transforming manufacturing industries do not apply to the same degree to pharmaceuticals. And while there is considerable debate about the precise costs of developing new drugs (an issue that will be revisited in chapter 7), there is little doubt that current expenditures easily run into several hundred million dollars.

Related to this is the second issue: Due to its subject – drugs for human bodies – pharmaceutical products are much less prone to rapid turnover. Clinical trials take many years and changes in consumer preference tastes cannot be satisfied as quickly as for other industries: Hence, it takes much more time to launch a new drug than a new cell phone. At the same time, once a therapeutic substance is launched on the market, it can be relatively easily copied. Therefore, despite the wild swings of capitalist free-market dynamism, pharmaceuticals – be they synthesized chemically or biotechnologically – have always been the subject of two specific sets of governmental interventions and regulatory regimes: Product approval and patents. Both are dealt with in detail in chapter 5**.**

2.2 Pre-R&D History

Throughout all societies and much of known human history, there had always been knowledge about substances to promote well-being and health. Yet a standardized,

industrial production of drugs took off only by the mid-nineteenth century when the medicinal effects of organic chemical substances, such as dyestuff, were discovered. Chemical companies in Switzerland (Ciba, Sandoz) and Germany (Hoechst, Bayer) first began launching standardized pharmaceutical products, such as Bayer's Aspirin in 1899. On the eve of World War I, German companies produced about 80 percent of the global pharmaceutical output. In the United States, synthetic pharmaceuticals were either imported from Germany or produced in German-owned U.S. plants (Steen 2001, p. 96). The first drug firms that were founded in the United States were not part of chemical conglomerates but started out as specialized pharmaceutical companies (e.g. Pfizer, Merck, Eli Lilly). Also they did not conduct systematic, formal research for drug development. Many crucial pharmacological breakthroughs, such as Alexander Fleming's discovery of penicillin as an antibiotic in 1928, were the result of accidents rather than of planned studies (Macfarlane 1985). It was only in response to the outbreak of World War II that the U.S. Government launched an extensive research and production program to translate the discovery of antibiotics and other compounds into large-scale drug production.

2.3 The 'Golden Age'

The large-scale production and commercialization of penicillin became a watershed for the pharmaceutical industry. Companies like Pfizer, which had accrued expertise in large-scale fermentation, garnered critical productivity gains. Recognizing that drug development could become a highly profitable business, big pharmaceutical firms established large-scale in-house R&D capacities (Pisano 2002, p. 349). As penicillin was one of the few drugs that

in fact cured diseases, after 1950 companies had a broad choice among a variety of unmet therapeutic needs. R&D programs were organized around the random screening of natural and chemically derived substances for their potential medical properties. Tens of thousands of compounds were screened before research would hone in on one 'lead' compound. Despite the limited knowledge of the biological underpinnings of diseases, and despite the role of serendipity, this process did lead to the development of new drugs in a 'target rich' environment over many years. In the 1950s and 1960s, also helped by the increase in public support for health-related research, pharmaceutical companies discovered a vast range of new chemical entities: From hydrocortisone and other hormonal products, to thiazide diuretic drugs against high blood pressure, tranquilizers, and the initial birth control products (Mazzucato and Dosi 2006, p. 3).

For pharmaceutical companies, the organizing principle of their R&D efforts was a large numbers' game, which is anything but random, but rather, a matter of internal organizational efficiency. Such institutionalized R&D setup based on economies of scale became part of the general culture of large drug companies: Centralized, hierarchical organizations that reaped the benefits of a management-led efficiency revolution (Chandler 1977). Companies were vertically integrated and developed in-house capacities for research, development, regulatory affairs, production, and marketing. Throughout more than three decades this organizational model allowed for a steady growth of the business into one of the most profitable industrial sectors. Pharmaceutical companies' rate of return on R&D investment on new drugs introduced in the United States between 1954 and 1978 was on average above 20 percent (Pisano 2002, p. 350). Yet its biological basis remained

thin: As of 1996, all the randomly sampled substances and the drugs developed on them addressed only 500 molecular targets in the human body out of a potentially 10,000 (Drews 2000). In the 1980s, returns on investment on random screening procedures started to decline. Not only was the pharmaceutical industry in need of alternative business strategies, it also needed a fundamental change in the *methods* of R&D.

2.4 The Age of 'Transformations'

The pharmaceutical industry's yearning for transformations coincided with the ascent of the biological sciences and their early commercialization by a budding biotechnology industry. As will be discussed below, the technical and scientific advances infused by the biotechnology industry also had organizational and geographical repercussions for the pharmaceutical industry. Conversely, the biotechnology industry profited from the large influx of money generated by hugely profitable pharmaceutical businesses.

Today, drug development involves three interrelated processes, each of which adds its distinct commercial value: the *search* for therapeutic 'targets', the *synthesis* of potentially therapeutic compounds, and the *screening* of those compounds for desired and unintended medical effects (Pisano, p. 348). Biotechnology consists of a bundle of different techniques, from DNA sequencing and gene splicing over antibody production. They enter the value-adding chain of drug development at different points. For instance, as the knowledge of biological processes and diseases increased, the search for new drugs became more 'rationally' geared towards potentially therapeutic compounds. In this vein, the

sequencing of the human genome promised to elucidate more of the genetic bases of diseases and to tailor drugs accordingly. As for the synthesis of drugs, with the exception of antibiotics, the overwhelming majority of them used to be small molecules that could be synthesized by processes established in organic chemistry. Only the invention of Recombinant DNA (rDNA) techniques by Herbert Boyer and Stanley Cohen in 1973 made it possible to produce larger therapeutic molecules such as insulin on an industrial scale. In contrast to most drugs that have a known structure and are chemically synthesized, these so-called 'biologics' are complex mixtures that are not easily identified or characterized. Biologics comprise products such as vaccines, blood components, monoclonal antibodies, or recombinant therapeutic proteins such as human insulin and growth hormones. Biologics currently account for basically all commercialized medicines that are synthesized by means of biotechnology (see 2.10 below).

The screening of medical effects profited from the combination of biotechnologies and advanced computer technologies. This synergy further tightened the feedback loops in drug development between rational design of drug candidates and their screening. Combinatorial chemistry, for example, allows for the synthesis of vast numbers of drug candidates, which in turn generates the need to speed up the screening process of such compounds. This is done by high throughput screening (HTS), developed as an automated, robotics-based technique for testing large numbers of substances. In combination with combinatorial chemistry, HTS is a return of the randomized screening principles, albeit much quicker and more productive thanks to the deployment of powerful computational routines.

Therefore, as drug discovery became more reliant on the scientific advancements in biology, contemporary drug development requires an unprecedented breadth of skills and approaches. The level of complexity has not only surpassed that of classical drug development, for which the predominant expertise used to be in medicinal chemistry, but it has also become too complex to be handled within one single company. Pharmaceutical companies began outsourcing certain tasks of this process, while honing their skills on how to incorporate the different parts into one coherent research program. Moreover, progress in one scientific field often had implications in another area. Firms wanting to capitalize on such cross-fertilizations increasingly have to have in place adequately flexible organizational mechanisms and structures. Taken together, these transformations have led to a post-fordist setup for pharmaceutical R&D that mirrors the changes in industrial production. Biotechnology played a role when drug development's technological, organizational and geographical setup changed. The centralized, hierarchical model of pharmaceutical companies that had all the capacities in-house was succeeded by decentralized, more networked organizational models of drug development. Crucially important for the point of this study, however, these changes in the organization of R&D did not change the logic of the drug business. Throughout all these transformations, pharmaceutical companies became even more focused on the marketing of blockbuster drugs worth billions of dollars in sales, in which they succeeded most profitably in the United States.

2.5 Trial and Error in Search of New Business Models

Incorporating these new technologies into existing business models for pharmaceuticals did not always prove successful. Conversely, in these times of transformation several new business models had been tried that had barely anything to do with advancements in technology. Whether or not they indeed provided a real competitive advantage, it is worth revisiting a few of Big Pharma's follies as they were part of the industry's creative destruction at work. While they reflect on the bounded rationality of allegedly rational business actors and their fear to miss the boat vis-à-vis competitors[8], they equally reflect on the old dictum that "the business of business is business."

To begin with, the late 1990s witnessed the rise of the 'life sciences' company. These companies tried to obtain a competitive advantage by applying modern biotechnologies to diverse products such as seeds, agrochemicals, specialized food products and human medicine under one corporate roof (Bijman 1999). Although there had undoubtedly been scientific synergies, financial analysts and stock markets did not appreciate the life science concept. It was not, that for example, the production of genetically modified seeds was unprofitable. Quite the contrary, as the U.S. company Monsanto demonstrated, which globally dominates the agricultural biotechnology business. But the profit expectations for drugs outpaced those for any other product. As a consequence, companies such as Monsanto and Novartis split their pharmaceutical from their agricultural business.

[8] For business fads driven by shareholder valuation considerations see also Zorn (2004).

Another strategy that gained momentum between 1993 and 1994 was the vertical integration of Big Pharma and drug merchants: Three major drug companies, Merck, SmithKline, and Eli Lilly acquired large-scale drug distribution intermediaries. These so-called Pharmacy Beneficiary Managers (PBMs) were seen as a strategic asset in selling the companies' own drugs, but also in obtaining full-scale information about drug consumption patterns, patients' and doctors' needs, and ultimately treatment effectiveness for the development of new medicines. Already two years later, however, Ely Lilly acknowledged a $2.4 billion write-down and that the price of $4.1 billion had been an overvaluation (Rangan 1998). In 2002, Merck decided to divest from its PBM arm Medco, which realized meager profit margins that dragged down the valuation of the entire company (Herper 2002). Like other companies that disbanded 'non-core' divisions, Merck decided to focus again on the development of new drugs.

Last but certainly not in the least, since the end of the 1990s the pharmaceutical industry went through several rounds of consolidation by mergers and acquisitions (Table 2.1).

Table 2.1: Top Pharmaceutical Merger & Acquisition Deals

Date	Target	Acquirer	Deal Value ($ billion)
4-Nov-99	Warner-Lambert (USA)	Pfizer (USA)	111.8
17-Jan-00	SmithKline Beecham (UK)	Glaxo Wellcome (UK)	79.6
26-Jan-04	Aventis (France)	Sanofi-Synthelabo (France)	71.3
26-Jan-09	Wyeth (USA)	Pfizer (USA)	68.1
15-Jul-02	Pharmacia (USA)	Pfizer (USA)	59.8
21-Jul-08	Genentech (44.2 %)	Roche (Switzerland)	45.7
9-Mar-09	Schering-Plough (USA)	Merck (USA)	41.1
9-Dec-98	Astra (UK)	Zeneca (UK)	39.9
17-May-99	Hoechst (France)	Rhone-Poulenc (France)	33.8
20-Dec-99	Pharmacia & Upjohn (USA)	Monsanto (USA)	31.9

Source: (Saigol 2009).

These mergers created gigantic corporations with a superior marketing power and global outreach. At the same time, their size alone did no longer guarantee innovative drug research. On the contrary, the old centralized, hierarchical drug development model that could reap efficiency benefits from large, centralized in-house R&D capacities had become an impediment. The merger mania was therefore accompanied by other organizational transformations, sometimes even by the same company. To overcome Big Pharma's stigma of an institutional culture that is too big and hostile to innovation, companies such as Pfizer, GlaxoSmithKline, and Roche all by splitting up in-house R&D. By creating competing clusters of innovative excellence, it was hoped that large pharmaceutical

companies could emulate the innovative nimbleness of the much smaller biotechnology firms (Kling 2009).

2.6 The Rise and Fall of Genomics

Genomics companies aim to exploit the science of the sequence and function of genomes. Relying heavily on advanced computational power, this business genre was sparked by the dramatic scientific breakthroughs in the course of the 1990s. Genomics was particularly boosted by efforts towards a complete sequencing of the human genome, which was achieved as the result of a collaborative yet competitive race between the publicly funded Human Genome Project (HGP) and a private corporation, Celera Genomics (Sunder Rajan 2003). As the first map of the human genetic information was published with much fanfare in March 2000, this created huge expectations that understanding the human blueprint would lead to a plethora of new diagnostics and drugs.

The high market valuation of genetic information had a systemic consequence: At least for a while, genomics companies were able to turn the table of the drug innovation regime. A new breed of biotechnology corporations carried out the leading edge research on genes, entire organisms' genomes, and their functions. They deploy techniques such as High-Throughput Screening, or screening by 'shotgun approach' (developed by Celera, the private competitor to the publicly funded Human Genome Project), all of which rely heavily on sophisticated computation. These approaches generate vast amounts of data and lend themselves to rationalization of research. Unlike the Chandlerian revolution for

managing production, which put large scale corporations at an advantage, this was a rationalization revolution in R&D. It was no longer carried out by the old masters of routinized innovation, large pharmaceutical firms, but by smaller competitors. Moreover, and this is the decisive difference to the times of Schumpeter, this time around routinized innovation also entailed routinized patent claims. Rising stars on the genomics horizon, companies such as Celera and Human Genome Science plastered the sequenced human genome with patents. Patents were filed despite the very limited knowledge about the utility of these gene sequences, as the majority of claims were targeting so-called Expressed Sequence Tags (ESTs) and Single Nucleotide Polymorphisms (SNPs). ESTs are parts of the nucleotide sequence that become visible when a gene is translated into a protein, no matter what function this protein has. SNPs are point mutations occuring at a rate of about one per thousand nucleotides along the human genome. SNPs can be extremely useful for identifying a person's genetic variance that correlates with their susceptibility to a disease and their response to a drug. Yet SNPs are mere marker of this and, like ESTs, do not necessarily reveal any bodily function.

Eventually, this Wild-West-style land grab of genetic information came to an end due to a number of developments. First, large pharmaceutical companies, as well as other actors engaged in biomedical research such as the Wellcome Trust, teamed up against the new gold-diggers and set up the so-called 'SNP-Consortium'. The purpose of this research consortium was to release into the public domain information about SNPs that may be relevant to drug development so that this information could no longer be patented (Lehmann and Lorch 1999). In other words, large pharmaceutical firms, normally very

keen on patenting their inventions, deliberately sacrificed intellectual property because of the fear that others – genomics companies – would block entire research alleys altogether. Second, the completion of the human genome draft sequence in 2000 placed a plethora of information in the public domain and could no longer be exploited commercially. Third, United States patenting guidelines for gene sequences became stricter. As of January 2001 gene sequences, including SNPs and ESTs, could only be claimed as intellectual property if the specific function and usefulness [9] of a gene sequence could be demonstrated (Krasner 2003). Fourth, it turned out that the human genome contained only 20,000–25,000 protein-coding genes instead of the originally assumed 100,000 (Human Genome Sequencing 2004), so that the relationship between genotype and phenotype was much more complex than initially anticipated. These developments together made genetic information as such less valuable. They also led to the depreciation of those companies that were selling their gene sequencing databases. What became increasingly relevant instead, was the linkage between information and downstream physiological and material conditions.

2.7 Geography and Destiny

The ascent of biotechnology also influenced strategic reorganization of pharmaceutical companies in terms of their geographical orientation. Until the end of the 1970s, the global drug industry was dominated by corporations like Merck (USA), Hoffman-LaRoche (Switzerland), Wellcome (U.K.), or Hoechst (Germany). These were multinational players,

but they still had a decidedly home-made tint with regards to where their innovations were made and where their products were marketed first. An extreme case was the industry of Japan: Japanese firms were large, but predominantly active in their domestic market, the second largest in the world. Lenient patent laws and protective pricing mechanisms allowed them to copy inventions elsewhere and reap the benefits domestically. Slowly, transitions started to set in when the first biotechnology companies such as Genentech, Biogen, and Amgen entered the U.S. market with their products in the early 1980s. As it became clear that most biotechnological discoveries that had commercial potential were first invented in the United States[10], the attention of the pharmaceutical industry increasingly focused on that country. Some European corporations entered R&D collaborations with university hospitals, for instance Hoechst[11]. Other large European pharmaceutical companies (Pharmacia; Hoffman-LaRoche) relocated vast part of their R&D activities directly into the traditional cluster of American pharmaceutical business in New Jersey. Yet the biggest bet on the future role of biotechnology for drug development was made by the Swiss firm Novartis, which bypassed the traditional pharmacy hub New Jersey and instead became established in San Francisco, San Diego, and Boston (Cooke 2005). Most indicative for Novartis' overall strategic R&D positioning was the decision to establish the company's primary pharmaceutical research arm in Cambridge, MA. Investing $4 billion, the Novartis Institutes for Biomedical Research (NIBR) opened in 2004 to target cardiovascular diseases, diabetes, infectious diseases, and oncology (Dyer

[9] For an invention to become patentable, it has to fulfill this 'utility' requirement. The history of patent laws as it became relevant for the biotechnology industry is discussed in more detail in section 5.6.
[10] The most notable exception being technologies related to monoclonal antibodies, which were first invented in the U.K.

2002). This decision epitomizes the crucial position of the United States for the current drug development logic: It unifies the diseases (all of which are concerns of affluent industrialized societies) with where the relevant technologies for these diseases are developed as well as where the company sees its most promising future markets.

As this study argues that biotechnology has become solidly embedded within the business models of a transformed pharmaceutical industry, I will next look at the global drug industry of today, taking into specific consideration the U.S. market, as well as the contribution of biotechnological drugs.

2.8 Current State of the Pharmaceutical Industry

In 2008, the global market for prescription drugs was worth $ 773 billion. Of this, North American sales accounted for 41 percent, $ 312 billion, alone (Table 2.2).

Table 2.2: 2008 Global Pharmaceutical Sales By Region

Region	**Sales (US$ billion)**
North America	312
Europe	248
Asia/Africa/Australia	91
Japan	77
Latin America	47
Total	773

Source: IMS Health: www.imshealth.com

[11] In exchange for Hoechst paying $ 67 million, the company obtained first rights to exploit commercially the research conducted at Harvard Medical School's Massachusetts General Hospital for a decade (Bud 1993, pp.

A recent list of the top 15 of global firms selling drugs (see Table 2.3 below) illustrates how much the global pharmaceutical industry has changed since the end of its 'Golden Age' in the 1970s. To begin with, the members of the global and the U.S. top sales charts are almost identical. Pharmaceutical companies that want to obtain a global leadership position can do so only by being successful on the American market. The notable exception is the German company Bayer, who is the world's 13th largest company while not being among the top 15 firms on the U.S. market. Yet Bayer is emblematic for how a once globally dominating German pharmaceutical industry these days has fallen behind into second-tier. Capitalism's creative destruction took its toll also on other leading German companies, such as Hoechst. The transformation of this chemical/drug company into a 'life science company' was not received well by shareholders and the subsequent spin-off of the pharmaceutical business deleted Hoechst from the top rank of global pharmaceutical businesses. Other international contenders, notably from Switzerland and the United Kingdom, have fared better and were able to vest themselves firmly among the top global players.

Two other major developments in the global pharmaceutical landscape are particularly noteworthy: Teva, an Israeli firm whose prime activity are generic drugs, demonstrates that such a business model can lead into the highest tier. And with Takeda now for the first time a Japanese firm ranks among the top sellers in the U.S. and globally.

204-5)

Table 2.3: Top Drug Corporations by Prescription Drug Sales 2008 (US$ Billion)

Rank Global	Company	Headquartered	Global Sales	US Sales	Rank US
1	Pfizer	USA	43.4	20.5	1
2	GlaxoSmithKline	UK	36.5	18.4	2
3	Novartis	Switzerland	36.2	12.4	8
4	Sanofi-Aventis	France	35.6	11.0	10
5	AstraZeneca	UK/Sweden	32.5	16.3	3
6	Hoffman-LaRoche (incl. Genentech)	Switzerland	30.3	13.1	7
7	Johnson & Johnson	USA	29.4	16.0	4
8	Merck	USA	26.2	15.5	5
9	Abbott	USA	19.5	10.0	11
10	Lilly	USA	19.1	11.4	9
11	Amgen	USA	15.8	13.4	6
12	Wyeth	USA	15.7	7.6	15
13	Bayer	Germany	15.7	4.5*	n.a.
14	Teva Pharmaceutical	Israel	15.3	9.2	12
15	Takeda	Japan	13.9	8.0	14

Table compiled by author; Source: IMS Health: www.imshealth.com

*including Canada (Bayer Annual Report: http://www.annualreport2008.bayer.com/en/Bayer-Management-Report-2008.pdfx)

2.9 The Global Dominance of the U.S. Biotechnology Industry

Despite the significant scientific capacities in European nations and the fear of competition from newly industrializing countries such as China, Korea, and Singapore (Segal 2004), a number of indicators confirm that the United States continues to be the dominant country for biotechnological innovation and commercialization. With regards to scientific output, scientific publications from the United States are cited more than those from the next seven countries combined (Ernst & Young 2007, p. 6). Likewise, most biotechnology patents, 43 percent of all, are issued in the US (ibid.). As a result, 70 percent of the global drug

development pipeline belongs to organizations headquartered in the United States (Moses III et al. 2005).

Also the commercial applications of biotechnologies are dominated by U.S. entities. Of all 4275 biotechnology companies in this world, one third (1452) are situated in the United States, more than in any other country (Ernst & Young 2007, p. 7). Despite efforts in other industrialized nations and support from governments, particularly in Europe, the number and economic range of specialized biotechnology startup-companies in the United States remains unparalleled (Dohse 2000; Nasto 2008). The U.S. dominance is even more pronounced when looking at the maturity and valuation of the companies: The country hosts 336 of the world's 710 (47 percent) publicly traded biotechnology firms (Ernst & Young 2007, p. 7). In 2005, these companies had a market capitalization worth about $400 billion, which was almost ten times that of European biotechnology firms ($43 billion) (Ernst & Young, 2007, Table p. 45). The global share for publicly traded U.S. firms was 69 percent of all biotechnology industry employees; 76 percent of all revenues; and 82 percent of all R&D expenditures (Ernst & Young, 2007, Top Table, p. 7).

The U.S. also remains the largest market for biotechnology drugs. In 2007, sales of biologics in the United States amounted to $41 billion, representing 56 percent of a global total of $75 billion products. By contrast, the five leading European countries together had a share of 24 percent, whereas Japan's share of global sales for biologics was 5 percent[12].

[12] IMS Health Reports: "News Release - Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding $75 Billion"; retrieved 07/10/2010 from http://imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=bba69e392879a110VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1

Therefore, for biotechnology drugs sales in the U.S. market are even more important than for prescription drugs in general (see 2.8 above).

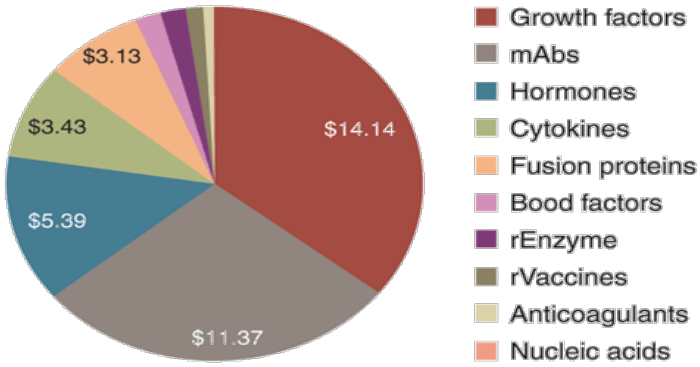
2.10 Big Pharma and Big Biotech

So far, few biotechnology entrants, all of which are engaged in the production and marketing of biologics, have managed to become fully integrated drug firms that could see eye to eye to Big Pharma. Among the global top 15 sellers of drugs, Amgen is the only biotechnology firm (see Table 2.3 above). At times spectacular, these commercial successes of a few selected biotechnology firms confirm, rather than challenge, the blockbuster drug model dominated by Big Pharma. The reasons for this are threefold: The concentration of market shares in few hands; the direct involvement of Big Pharma; and the high prices for biologics.

First, biologics continue to be a small and concentrated subdivision of the pharmaceutical market. Collectively, in the United States the sales of biologics rose from $18.9 billion in 2002 up to $40 billion in 2006, which was under 15 percent of all prescription drugs (Aggarwal 2007, p. 1097). Two categories of biologics, growth factors and monoclonal antibodies[13], account for more than $25 billion alone (Figure 2.1).

[13] Growth factors include erythropoietins, which stimulate red blood cell formation, and colony-stimulating factors, which are used in oncology. Monoclonal antibodies (mAbs) are used for various indications, ranging from Crohn's disease and rheumatoid arthritis to colon and breast cancer.

Figure 2.1: Top Ten Categories of Biologic Drugs in Terms of U.S. Sales in 2006



	2005 US sales ($ billions)	2006 US sales ($ billions)	2005 growth (%)	2006 growth (%)
Growth factors	12.11	14.14	10	17
mAbs	8.29	11.37	38	37
Hormones	4.51	5.39	24	19
Cytokines	3.11	3.43	4	10
Fusion proteins	2.81	3.13	36	11
Blood factors	0.74	0.78	11	5
rEnzyme	0.58	0.76	18	31
rVaccines	0.40	0.56	–10	40
Anticoagulants	0.34	0.34	–1	–1
Nucleic acids	0.06	0.02	–	–

Source: (Aggarwal 2007, p. 1098)

This market segment is overwhelmingly dominated by two companies, Amgen and Genentech (see Table 2.4). Not only do these two firms have by far the largest revenues, they also account for over two-thirds of profits of all U.S. biotechnology firms (as a majority is still loss-making).

Table 2.4: Top U.S. Biotechnology Firms (2006 Data)

Rank	Company	Headquartered	Revenue (US$ million)	Net Income (Loss) (US$ million)
1	Amgen	Thousand Oaks, CA	14,268	2,950
2	Genentech*	San Francisco, CA	9,284	2,113
3	Genzyme	Cambridge, MA	3,187	($17)
4	Gilead Sciences	Foster City, CA	3,026	($1,190)
5	Biogen Idec	Cambridge, MA	2,683	$218
6	MedImmune**	Gaithersburg, MD	1,277	$49
7	Sepracor	Marlborough, MA	1,197	$185
8	Celgene	Summit, NJ	899	$69

*Became a wholly owned subsidiary of Hoffman LaRoche in 2009
** Became a wholly owned subsidiary of AstraZeneca in 2007

Source: (Ernst & Young 2007, p. 18)

Second, in addition to the original biotechnology contenders, also large pharmaceutical firms have taken an interest in the field of biologics (see Figure 2.2), bringing with them the financial resources and the market expectations of the blockbuster drug business. Big pharmaceutical companies constantly have to fill their pipelines with new drugs to upkeep their shareholder value. Patent protection for some of the top revenue generators, products such as the world's bestselling drug Lipitor (see Table 2.6 below) will expire soon and revenues will go to generic manufacturers.[14] Biologics seem to become a lucrative alternative for several reasons. Because of their intricate – biological – structure, biologics are harder to copy, so that generic versions (so-called 'biosimilars') cannot take over the market as quickly once the drug patent expires.

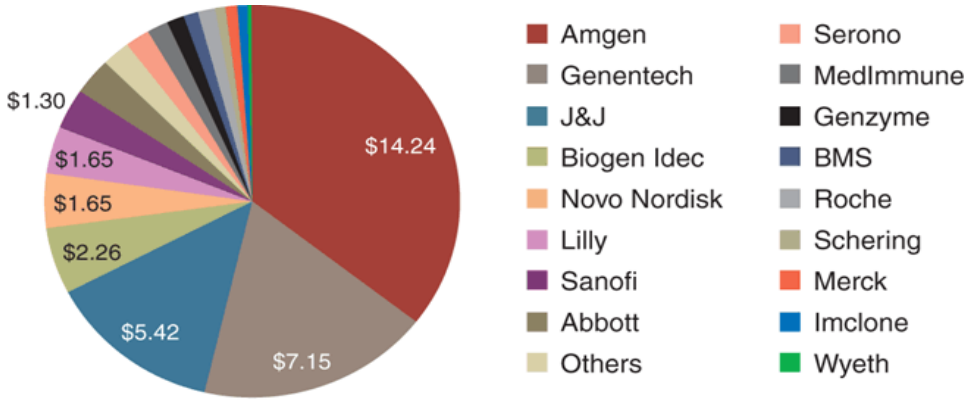
[14] It is estimated that about half of the currently patented drugs sold globally will lose patent protection within the next five years. In 2010 alone, the pharmaceutical industry is estimated to lose 15 percent of its revenues from patented drugs (Anonymous 2009).

Moreover, there are already a number of biologics developed by biotechnology firms on the market that have proven to work. Investing in their marketing reduces the risk for big pharmaceutical firms of late-stage R&D failure. Marketing biologics dovetails with a general trend in the pharmaceutical industry, which since the 1980s, increasingly filled its pipeline with in-licensed rather than with in-house developed technologies (Booth and Zemmel 2004).

Another way to keep the pipeline filled is to acquire the entire company wholesale. In recent times therefore, a number of takeovers worth billions of dollars of biotechnology companies by big pharmaceutical firms took place. Some acquisitions went as smoothly as the $8.8 billion takeover of Millennium by Takeda, and the $15.6 deal between AstraZeneca and MedImmune. In other cases, biotechnology companies dreaded the acquisition from Big Pharma. Fearing to loose their distinct innovative value and corporate identity, ImClone and Genentech refused the bids of Bristol-Myers Squibb (BMS) and Roche, respectively. Although both were ultimately acquired by large pharmaceutical companies[15], their resilience also demonstrates the limits of a full-blown integration of biotechnology into the world of Big Pharma: Both needs but does not necessarily like each other. Differences in attitudes and clashes in business culture still continue to be a divisive issue between Big Pharma and biotechnology firms, even the biggest ones.

[15] Roche, which owned a majority of Genentech since 1990, ultimately acquired the remaining 44.2 percent of shares for $46.8 billion in March 2009. ImClone accepted a higher bid by Eli Lilly and was formally acquired for $6.5 billion in November 2008 (Pollack 2009).

Figure 2.2: Top Companies and Sales of Biologics in the U.S. in 2006



	2005 US sales ($ billions)	2006 US sales ($ billions)	2005 growth (%)	2006 growth (%)
Amgen	11.79	14.24	22	21
Genentech	4.37	7.15	97	64
J&J	5.21	5.42	–2	–9
Biogen Idec	1.99	2.26	14	13
Novo Nordisk	1.38	1.65	32	20
Lilly	1.82	1.65	–1	4
Sanofi	0.98	1.30	46	33
Abbott	0.86	1.21	57	41
Serono	0.67	0.78	13	17
MedImmune (now Astra Zeneca)	0.67	0.73	14	9

J&J: Johnson & Johnson; BMS: Bristol-Myers Squibb

Source: (Aggarwal 2007, p. 1099)

A third reason why biologics confirm the blockbuster drug logic is that these drugs are sold with a steep premium. Biologics come at a price that begins above $1,000 per dose and can reach up to $100,000 for the most recent cancer drugs (Table 2.5).

Table 2.5: Selected Biologics and Costs

Product	Indication	Average Monthly Cost*
Zevalin (ibritumomab)	Lymphoma	$24,000
Erbitux (cetuximab)	Colorectal cancer	$17,000
Cerezyme (imiglucerase)	Gaucher disease	$15,000
Avastin (bevacizumab)	Colorectal cancer	$4,400–$8,333
Zavesca (miglustat)	Gaucher disease	$4,200
Herceptin (trastuzumab)	Breast cancer	$3,250

*Dosing duration of all medicines is highly variable, but most regimens require at least one month.

Source: (Herrera 2006, p. 259)

Proponents of the high costs for biologics argue that, because they reach only a smaller population, the costs for society at large would not be bigger. One particularly contentious issue are the prices for cancer drugs. Price-setting for drugs that are administered only at the end of a person's life is not a rational matter of supply and demand, but a rather emotional test of society's 'absorption capacity' of costs[16]. In addition, biotechnology companies also pursue a strategy that is known from regular pharmaceutical companies: Instead of inventing new drugs, it is more rewarding to extend the group of patients with a different disease to be treated with the same biologics[17]. For all these reasons, in the United States sales of biologics have become the fastest rising segment of the pharmaceutical business. Such biologics push up the expenses for healthcare plans and employers decide to include them only in the most expensive of their pharmaceutical benefit plans, to which only a small population of employees has access (Elswick 2003). Despite the exclusive

[16] Pushing the limits by justifying the abovementioned costs for Avastin of above $8,000 monthly, an executive of Genentech stated that Genentech had set the price based on "*the value of innovation, and the value of new therapies.*" (as quoted in Berenson (2006)).

[17] For example Genentech (now part of Hoffman LaRoche) aims to extend the FDA approval for its anti-cancer-drug Avastin. This biologics is currently only approved for late-stage colon, breast and lung cancer, where it has shown to prolong life by up to a few months. Avastin's admission for treating earlier stages of cancer would further increase its $2.7 billion of sales in the United States (Pollack 2009).

availability, recent sales figures confirm that a few, selected 'blockbuster biologics', such as Enbrel, Neulasta, Epogen, and Remicade, are now in the same league as 'regular', chemically derived, top-selling pharmaceuticals in the United States (Table 2.6). If anything, biologics have brought the blockbuster drug logic of big pharmaceutical companies to a new level.

Table 2.6: Top US Pharmaceutical Products by Sales 2008

Rank	Brand	Therapeutic Class	Sales (U.S.$ billion)	Company
1	Lipitor	Lipid Regulator	7.8	Pfizer
2	Nexium	Proton Pump Inhibitor	5.9	AstraZeneca
3	Plavix	Anti-Platelet	4.9	Bristol-Myers Squibb/Sanofi-Aventis
4	Advair Diskus	Steroid, Inhaled	4.4	GlaxoSmithKline
5	Seroquel	Anti-Psychotic	3.9	AstraZeneca
6	Singulair	Anti-Asthma	3.5	Merck
7	Enbrel	Anti-Athritic*	3.4	Abbott/Amgen/Wyeth
8	Neulasta	Colony Stimulating Factor*	3.1	Amgen
9	Actos	Diabetes medication, Oral	3.1	Takeda
10	Epogen	Erythropoeitin*	3.1	Amgen
11	Prevacid	Proton Pump Inhibitor	3.1	Takeda
12	Abilify	Antipsychotic	3.1	Otsuka/Bristol-Myers Squibb
13	Remicade	Anti-Athritic*	3.1	Johnson & Johnson
14	Effexor	Antidepressant	3.0	Wyeth
15	Lexapro	Antidepressant	2.7	Forest Pharmaceuticals

* Biologics

Table compiled by author; Source: IMS Health: www.imshealth.com

2.11 Conclusions

To come back to the initial argument of this section: The commercial successes of a number of companies and their biologics corroborate the blockbuster drug logic. With Genentech being fully acquired by Roche, to date Amgen is the only remaining independent large biotechnology company in the league of Big Pharma. Despite the stylized ‘clash of cultures’, biotechnology and pharmaceutical companies have a symbiotic relationship. Large pharmaceutical companies, no longer able to invent enough profitable drugs in-house, are in constant need of new technologies to fill their drug development pipeline. They often pay a steep premium, certainly for approved drugs, to biotechnology companies. A part of this quest is responsible for the organizational and geographical transformation that the pharmaceutical industry witnessed. Another reason for the geographic and organizational restructuring is the concentration of market power in the United States. It is the most lucrative market for drugs, conventional and biological. Global drug leaders and leaders in the US market have become increasingly synonymous.

The next chapter will complement these results by adding the views of the biotechnology industry community. They will for instance explain how biotechnology companies depend on the contractual agreements they have with big pharmaceutical players, and increasingly so the closer a technology comes to being sold on the market. They will also spell out the reasons for the industry being clustered in specific regions

Chapter 3: Theoretical Approaches Towards Analyzing Biotechnology

> *"Americans of the late twentieth century have been conditioned to see free enterprise and government noninterference as virtues so compelling and self-evident that they must have been the goals of our revolutionary forbearers."* (John L. Larson, Internal Improvement: National Public Works and the Promise of Popular Government in the early United States, 2001)

3.1 The Limitations of Neoliberal Frameworks to Analyze Biotechnology

Neoliberal economists and policy makers regularly focus on technological innovation as the most crucial dimension of economic success (Steil, Victor, and Nelson 2002). This view has also informed many analyses of the biotechnology industry, either in business studies (Oliver 2003; Robbins-Roth 2000), by economists (Pisano 2002), or political scientists (Giesecke 2001; Hart 2003). Taking neoliberalism seriously means taking the economic motivations and business strategies of individual firms as the starting point. It is they who are supposed to drive economic growth and well-being. This study will do so on three theoretical accounts: First, I will revisit the concepts of Joseph Schumpeter and capitalism's perennial gale of creative destruction (3.2). His concepts are particularly relevant for claim 1, to prove that biotechnology did not have a revolutionizing economic impact. Second, I will turn to the historical and substantive aspects of neoliberal concepts (3.3). Neoliberal transformations that entailed ideology, financial orthodoxy, a globalizing

economy, and a leaner, but more competitive state apparatus, provided the backdrop against which the ascent of the industry in the United States took place. Third, by making reference to the approach to study varieties of capitalism, I will put the individual firm at the center of my analysis (3.4). My study will be scrutinizing whether the comparative institutional advantage of the United States for the biotechnology industry falls in line with what the VoC-approach postulates. Shortcomings of VoC that are not only of a general matter, but also with regards to an analysis of the biotechnology industry will have to be addressed. This includes alternative theoretical frameworks that have been applied in previous studies on the biotechnology industry. Some substitute VoC's view of the firm as a relational, rational actor with sociologically informed approaches that look at the social embeddedness of the firm (3.5). Others have put a different emphasis on the institutional support structure and gave it the term 'national innovation systems' (3.6). These approaches will bring clarity into the comparative advantage that certain clusters in the United States have domestically as well as internationally. Yet they continue to be neoliberal frames of reference in the sense that also they ignore to what extent the comparative advantage for biotechnologies is determined by the shape of the demand side in the United States (3.7). Complementarities between the United States' liberal market economy and biotechnology should therefore be extended to the provision of healthcare. As the concluding section (3.8) points out, successful neoliberal policies to unleash the generation of biotechnological innovation, were incumbent on the institutional setup the United States' deregulated, fragmented healthcare system, whose negative side effects became a politically contested issue only recently.

3.2 Schumpeter's Core Concepts and their Importance for Biotechnology Innovation

As a consequence of the neoliberal ideological and political turn that found support of the supply-side in economics critical, Joseph Schumpeter's ideas about the importance of innovation for capitalism were rediscovered[18]. Be it the invention of new products, or new methods of production or transportation, new markets, and new forms of industrial organization: They all illustrate the same process of industrial mutation, which

> *"incessantly revolutionizes the economic structure* from within, *incessantly destroying the old one, incessantly creating a new one. This process of Creative Destruction is the essential fact about capitalism…Every piece of business strategy acquires its true significance only…*[and] *must be seen in its role in the perennial gale of creative destruction."* (Schumpeter 1942, p. 83)

Schumpeter's ideas about the role of innovation in capitalism opens an array of research questions for my subsequent analysis of the biotechnology industry:

First, how does capitalism's potential for 'creative destruction' play out within and among companies of the biotechnology industry? What actually is *created* and what is *destroyed*? While Lichtenberg (2006) undertook a systematic, econometric analysis of pharmaceutical innovation as a process of creative destruction, so far the biotechnology industry has not

[18] Obviously, Karl Marx was much aware of the pivotal role of technology in capitalism. However, his focus of attention was the role that technologies played for the relations between labor and capitalist.

been scrutinized applying the Schumpeterian paradigm. Also, contemporary scholars redefined the concept of 'creative destruction.' Breschi et. al (2000) suggested that where there are large, established firms, new entrants have to overcome high barriers In those cases it is not 'creative destruction' that shapes an industry, but 'creative accumulation'[19].

Second, Schumpeter claims that capitalism has gone through different lengths of innovative business cycles depending on the degree of creative destruction that certain innovations have brought about (Schumpeter 1964)[20]. But how disruptive for the various cycles of businesses has biotechnology really been so far? Widely disruptive powers of biotechnology have been applauded (Oliver 2003) or feared (Rifkin 1998), while others have been more skeptical about biotechnology's revolutionary potential (Fransman, Junne, and Roobeek 1995; Nightingale and Martin 2004). This study will extend such skepticism and demonstrate that biotechnology so far has not had a revolutionary impact. Yet any analysis of the biotechnology industry (including this one) has to address biotechnology's cyclicality: What are the reasons that the several booms of financial excitement about biotechnology were followed by collapses in valuation of the entire industry?

Third, zooming in on this problem, how have 'boom and bust' cycles in biotechnology innovation unfolded? In Schumpeter's theory, innovative, 'first mover' enterprises can muster huge profits from the temporary monopoly power of their innovations, largely due to the destruction of competitors. But not for long, as the exceptional profits attract

[19] Note that creative accumulation does not necessarily have to be an optimal outcome, as path dependence (see section 1.5) can lock in sub-optimal technologies

imitators who copy successful 'first movers.' Low-risk, profit-seeking imitation first leads to an upswing of innovative activity, but the boom is soon to be followed by a downswing. This flogging instinct and the fear of missing out on a crucial round of technological innovation had already been addressed with regards to the wax and wane of the genomics industry (see 2.6 above). The reality of that boom-and-bust cycle was also more complicated, because imitating innovation in biotechnologies is inhibited through intellectual property protection.

Fourth, what is the relevance of the organizational setting for innovation? For Schumpeter (1934), the engine of innovation and growth was the heroic, risk-taking entrepreneur, a pioneer with an imaginary mind. But as firms grow, serendipity in innovation would be increasingly substituted by routine. Entrepreneurs, by means of spreading enlightenment ideas of rationalization, therefore undermine the very source, the spirit of entrepreneurial innovation (ibid., p.132). The modern corporate manager that evolved would become the antithesis of the original entrepreneur, leading to large, hierarchical, rationalized corporations, which capitalize on their rationalization gains thanks to the visible hand of a revolution in management (Chandler 1977).

However, one should not per se assume the superiority of large-scale enterprises when it comes to organizing research and development: Large firms' economies of scale advantage for routinized innovation may partially or even fully be offset by their hierarchical,

[20] Such rearrangements include 3-year long Kitchin cycles, caused by the de/accumulation of inventory; 8 to 11 year long Juglar cycles, caused by individual innovations such as the dynamo; and the 50 to 60 year long Kondratieff cycles, which are brought about by major innovations such as the railroad.

centralized, bureaucratic structures (Nelson and Winter 1982, p. 279). The question of limits for 'routinized innovation' as described by Schumpeter is all the more important because of the specific features of the field of biomedical science: Unlike for example a new microchip, which can still be improved after an unsatisfactory test run, this is hardly the case for a new drug: A molecule either works or it does not. A drug candidate that is developed and tested in the laboratory for many years and then fails the final testing in human beings will have to be discarded and never reaches the market. As production costs are almost negligible, expenditures that go into discovery of new drugs become the key factor. But where and how to invest is a question to which different answers have been given at different times. These investment decisions are part of the business logic of the biotechnology industry. It is the inherent risk of drug development, which is at the center of the co-evolution and the 'cultural clash' between allegedly venturous start-up biotechnology entrepreneurs and the bureaucratic representative of Big Pharma. This conflict will feature prominently during many of the interviews with entrepreneurs of the biotechnology industry (see 4.5), which saw their own innovative image clashing with that of bureaucratized Big Pharma.

Fifth, is there a role for government intervention in the perennial gale of creative destruction? Schumpeter did not make any prescriptions with regards to government intervening in the creation of innovation[21]. He only explained that government should not intervene to prevent monopolies as they are the price that has to pay for the vast economic gains that large-scale corporations bestow upon society. More generally, Schumpeter

assumed the pre-existence of innovative firms. This turns out to be a serious shortcoming of Schumpeter's theory, because the question of what an innovative environment should exactly look like continues to motivate scholars and policy makers alike until this date. Consequently, chapter 4 and 5 will discuss a range of policies to stimulate biotechnology firms in the United States.

3.3 The Neoliberal Turn

The concept of neoliberalism is open to various conflicting interpretations. Many of them have to do with the ambiguity of the term 'liberalism', which harks back to 'liberty' and its individual feature as opposed to a more holistic view on society[22]. Classic liberalism took heed from Adam Smith's observations about human's *"propensity to truck, barter and exchange one thing for another"* (Smith 1937, p. 12). His 'invisible hand of the market' was interpreted as a prescription for economic *laissez-faire* policies, most prominently free trade and a minimalist state. In times of classical liberalism, the intended 'unintended' consequence of individual wealth production would be wealth production for the society as a whole. Yet Smith himself, being a lecturer of moral philosophy, never used the notion of *laissez-faire.* He believed that the pursuit of individual interests be conducted in socially

[21] Hospers (2005) therefore concludes that *"[t]he case Schumpeter makes is not* for *the market and* against *intervention in general; it is rather a case for intervention adapted to the particular circumstances of time and space."* (p. 33).

[22] To this date, a 'liberal' in continental Europe is generally conceived as a conservative concerned with his own economic liberty. By contrast, the counterpart in the United States is label for a moderately left-of-center view. Another important divide exists between the concept of neoliberal institutionalism, where the hegemonic economic power is replaced by a range of regimes (Keohane 1984). For an overview of different liberal and neoliberal interpretations see Cerny (2005).

controlled forms guided by sociocultural, legal, and organizational rules (Trigilia 2002, p. 22).

Therefore, substantially not so much different is the assumption of neoliberalism that human well-being

> "*can best be advanced by liberating individual entrepreneurial freedoms and skills within an institutional framework characterized by strong private property rights, free markets, and free trade"*(Harvey 2005, p.2).

Neoliberalism as a political *concept* was first formulated by Friedrich August von Hayek in 1944. To avoid"*The Road to Serfdom"* (1944) requires two institutional safeguards: The limited power of the state and a free economy. Yet as a political *project* it was lingering on[23] until political leaders looked for economic responses to the crisis of accumulation in the 1970s. Until then, the post World War II economic model of capitalist societies, the 'Golden Age' of capitalism established under American leadership, enjoyed relatively broad legitimacy due to features such as: A compromise across classes and ideologies and shared common ideas about governments' role for full employment; Keynesian strategies for economic stability and growth that relied on the demand side of the economy, such as safeguarding the purchasing power of vast parts of the population for mass-produced

[23] It was, however, developed further in academia and in think tanks, most prominently the Mont Pelerin Society (MPS). Among MPS's illustrious members were for instance, Michael Polanyi (Karl's younger brother), Milton Friedman, and Karl Popper. Also today, the MPS continues to warn about the *"danger in the expansion of government, not least in state welfare, in the power of trade unions and business monopoly, and in the continuing threat and reality of inflation"* See http://www.montpelerin.org/home.cfm, visited 6/12/2009.

goods; Strengthening labor interests over those of capital; de-commodifying and extending the welfare state; and an international trade system open enough to support domestic industries geared for exports and protectionist enough to avert harm to other sectors (Streeck and Thelen 2009, p. 97).

The crisis of capital accumulation in industrialized capitalist economies was caused by a variety of coinciding factors that cumulated in the 1970s (increasing oil prices, surge in labor resistance, and the budgetary burden of an extended welfare state). Neoliberal policy shifts affected all of the abovementioned aspects of the compromise and the glue that made possible the long boom of capitalism from the late 1940s to the early 1970s.

In the following, I will address several key dimensions of neoliberal transformations: Ideology; Financial Orthodoxy; Economic Globalization; Changing Role of the State. As they have affected many countries, they will be presented first on a general level, before I present the specific circumstances in which they took place in the United States. This way, the political and ideological changes will be drawn that affected the rise of the biotechnology industry in the United States.

Ideology

Neoliberal transformation implied the increased marketization of society. As public, social needs were considered to be met best by private means coordinated by market forces, politics and policy-making on the domestic and on the international level should be geared

towards a well functioning of markets (Cerny, Menz, and Soederberg 2005, p. 12). Ultimately, by emphasizing the significance of contractual relations in the marketplace

> *"neoliberalism values market exchange as an ethic in itself, capable of acting as a guide to all human action, and substituting for all other ethical beliefs... It holds that the social good will be maximized by maximizing the reach and frequency of market transactions, and it seeks to bring all human action into the domain of the market."* (Harvey 2005, p. 3).

The United States may historically have always been dominated by a culture of individualistic, market-oriented behavior. For instance, in no other industrialized country has the 'marketization of health' reached the level of the United States. But also here there are leftovers of the Keynesian welfare state that underwent neoliberal improvements, such as President Clinton's campaign for 'ending welfare as we know it'.

As will be discussed in subsequent chapters, the evolution of an ethics of market exchange has been at the heart of advancements in biotechnology. Questions about the commodification of living matter, and for what purpose, for instance the patenting cell lines or genetic information have turned out to be crucial stumbling blocks – or accelerators - for the industry.

Financial Orthodoxy

Another key dimension of neoliberal politics was the shift away from Keynesian macroeconomic demand management towards a supply-side approach to macroeconomic management. It argues that overall economic wellbeing is maximized when the barriers to producing goods and services (the 'supply side' of the economy) are lowered. Consumers would then benefit from a greater supply of goods and services at lower prices. Supply-side policies would typically lower taxes for corporations and for individuals, particularly in the higher bracket, in the expectation that this would free private capital to be invested. Moreover, the role of fiscal policies would generally be lessened in favor of monetarist interventions to curb inflation[24].

In the United States this era began when the Federal Reserve Bank raised the interest rate to almost 20 percent until 1981 to regain stability for the currency. This 'Volcker shock' triggered a recession in the tailwind of which unemployment rose to over ten percent (Harvey 2005, p. 23). When Ronald Reagan entered the White House in 1981, he unleashed a range of initiatives to deregulate businesses, cut federal budgets and taxes, and to attack organized labor. Reagan's specific way towards neoliberalism was to combine all these measures with a huge increase in military expenditures. In fact these policies can be interpreted as another 'Keynesian compromise': Preoccupied with the Cold War, Reagan

[24] A third tenet of financial orthodoxy was balanced budgets. Yet while this entered developing countries' structural adjustment policies prescribed by the Bretton Woods Institutions, advanced capitalist countries did not heed this advice. Many European countries regularly violate the threshold for the budgetary deficit of 3 percent of Gross Domestic Product that he European Union's Stability and Growth Pact requires (Cerny, Menz, and Soederberg 2005, p. 16). And in the United States, unprecedented levels of deficit have piled up under presidents Ronald Reagan (averaging 4.2 percent of GDP) and George W. Bush (who turned a 1.9 percent surplus into a 3.4 percent deficit at the end of his presidency. See http://www.usgovernmentspending.com/federal_deficit_chart.html).

launched a deficit-funded arms race ('Military Keynesianism') that specifically benefitted his electoral majority in the West and the South of the United States (Harvey, p. 88). The way in which these military resources were allocated became also consequential for the amassing of financial and scientific resources that profited the biotechnology industry (see chapter 5).

A Globalizing Economy

From its beginning in the 1970s, neoliberal transformations have also had the purpose to open up the global economy. This included liberalization of trade, increase in transboundary flows of capital and investments, and the internationalization of production. Some studies that looked at national economies and the effects of neoliberalization on them have been using the term synonymously with economic globalization[25]. Others, looking outward-bound to the same dynamic, have defined economic globalization with regards to the integration of national economies into the international economy through trade, direct foreign investment, short-term capital flows, international flows of human resources, and flows of technology (Bhagwati 2004, p.3).

Why is this relevant for an analysis of the biotechnology industry? Biotechnological sciences are not so much dependent on material input than on knowledge. Knowledge-intense industries have become embattled assets in a globalizing economy, because in theory, they are more footloose and are movable more rapidly than material production facilities (Hilpert 2003). This is the case, for instance for information and

[25] See for instance Greider (1998), Mittelman (2000), or Tabb (2001).

telecommunication technologies, where new hubs have sprung up from Dublin to Bangalore. In comparison, the medical biotechnology industry remains concentrated where it started out: Not only are the major producers of advanced technologies clustered in a few regions in the United States, but the majority of their products are geared for the United States too (see section 2.8). This, however, is not to say that biotechnology contradicts the dynamic of economic globalization. Rather, my study analyzes the reasons for how and why biotechnological innovations have become concentrated within a few local clusters in the United States, and how this has affected the global architecture of drug development and commercialization. My reasoning is similar to Saskia Sassen's analysis of centers of global finance that shape the global financial architecture (2001). Her account of these 'global cities' reveals as much about the reconfiguration of global actors in a local space, as it analyzes the implications of their activities for the global financial architecture. Innovations in finance and in biotechnology, therefore, reflect the *"deterritorialization and reterritorialization of socio-economic and political space"* (Held et al. 1999, p. 27). Seen that way, globalization is a highly uneven process that

> *"both reflects existing patterns of inequality and hierarchy while also generating new patterns of inclusion and exclusion, new winners and losers…globalization, thus, can be understood as embodying processes of structuration and stratification."* (ibid.)

Also the global dissemination of biotechnologies reflects new patterns of winners and losers, both among private and public entities, as well as within countries in the industrialized North and the developing South (Pistorius and van Wijk 1999; Lehmann

2001). Such ‘transformationalist’ assumes that economic globalization does not reflect a single logic of development: Neither does it bring about a borderless network economy (Kelly 1998), nor a level-playing field (Friedman 2005), or even a stateless world (Ohmae 1995). I argue that it is not *despite* globalization pressures, but rather *because* of them, that the United States (or, to be more precise, certain clusters in that country) remains the most competitive location for the global biotechnology industry. And while other countries, and their governments and bureaucracies, have made efforts to catch up, they have not yet succeeded. Such absence of convergence among capitalist countries is an issue that will be revisited again (see 3.4 below), when we look at the varieties of capitalism.

The Competitive Nation-State

Another important dimension of neoliberal transformations can be seen in the change in tasks for the states, both domestically and internationally. Throughout the economic boom after World War II, it was generally accepted that governments had a role to play in policies to stimulate economic growth, full employment, the promotion of industrialization, and to a certain degree, redistribution of wealth through progressive fiscal policies and the welfare state (Cerny et al., 2005, p. 17). By contrast, the neoliberal state was supposed to recede from all these tasks: It should not intervene to achieve a particular outcome, but rather set the regulatory framework for a level-playing field among market actors. As an arms-length regulator, “Governments should steer but not row” (Osborne and Gaebler 1992).

Yet whereas neoliberals in the 1970s and the 1980s were requesting the state from withdrawing from intervening more or less entirely, the requests changed: Intrusions of the state became no longer contested, they were even demanded, as long as they served an entrepreneurial, pro-market purpose. At the same time, social policies are to be subordinated to economic policies (Jessop 2002). The biotechnology industry is a thankful study object for how actors who claim to profit from an unfettered market economy, and who rhetorically often rejecting state intervention, at the same time demand the state to intervene, among other things to safeguard private property rights, the rule of law, the functioning of markets and free trade.

Moreover, owed to the fact that neoliberalism is an explicitly globally oriented endeavor, the neoliberal state should strive for internal reorganizations and institutional arrangements to improve its competitive position in the global market in comparison with other countries (Harvey, p. 65). Globalization has not brought about the *"end of the state"*, but has encouraged *"a spectrum of adjustment strategies and, in certain respects, a more activist state"* (Held, et.al., p. 9). Instead of a withering away of the state, changes towards a more activist state are undertaken to compete with other nations to accommodate better the needs of capital. In such a 'leaner meaner' state

> *"the capacity to deliver services that the affluent can supply privately for themselves (e.g. health and education) is sacrificed while the more restricted institutional capacity necessary to deliver essential business services and security (domestic and global) is maintained*." (Evans 1998, p. 23)

Putting it another way, the state is not retreating, but is rather changing its *mode* of authority to become a 'competitive nation-state' (Hirsch 1995). The state retreats from providing domestic welfare directly, from wielding ownership in key industries and infrastructural services, from maintaining full employment. Instead, state capacities are extended to attract foreign capital, to marketize and privatize economic and social activities, and to embed the state in transboundary economic practices and its legal institutions (Cerny, Menz, and Soederberg 2005, p. 5).

All these adjustment strategies can be studied in the development of biotechnology. My study will address the effects of a range of pro-market, pro-entrepreneurial policies devised by the US government throughout the historical development of the biotechnology industry. Equally important, such measures were taken to stem the tide of a declining competitiveness of the US industry and economy. Yet economic growth driven by technological and scientific knowledge call for a very different set of enforcement tools compared to one in which industrial production is driven predominantly by material input. The enforcement of intellectual property rights becomes a crucial case in point. Patents call for an active state on the inside, and a pro-active, state on the outside to safeguard the compliance of other states to its rules. Therefore, instead of a 'night watch state' that is hands-off, the most sophisticated economic actors need a hands-on state as a sophisticated active enforcer (Evans, 1998, ibid.) of certain market mechanisms. Such interventions had and continued to have a crucial influence, which was not limited to the domestic sphere. As neoliberal institutionalists such as Keohane and Nye (1989) and Ikenberry (2001) have

pointed out, post World War II international institutions were significantly shaped by United States' interests and interventions. Some of the most relevant multilateral organizations have been established as an expression of the United States' hegemony (Foot, MacFarlane, and Mastanduno 2003), a topic that will be revisited when looking at the establishment of international trade agreements and intellectual property regimes pertaining to biotechnological innovations (see 7.5 below).

Whereas the sum of the above neoliberal policy prescriptions turned out to be only mildly effective in revitalizing global capital accumulation[26], a broader ideological transformation gained traction not only in the United States, but in quarters as diverse as the United Kingdom under Margaret Thatcher, China under Deng Xiao Ping, and Chile during the dictatorship of Augusto Pinochet. Harvey therefore concludes that

> *"Neoliberalism has not been very effective in revitalizing global capital accumulation, but it succeeded remarkably well in restoring, or in some instances (as in Russia and China) creating, the power of an economic elite…The evidence suggests, moreover, that when neoliberal principles clash with the need to restore or sustain elite power, then the principles are either abandoned or become so twisted as to be unrecognizable."* (Harvey 2005, p. 19)

[26] As a matter of fact, both in the UK under Margaret Thatcher and in the United States under Ronald Reagan, the first years of neoliberal policy turnaround were characterized by a recessions.

By now it should have become clear that at least in a number of advanced capitalist countries the transformations that took place showed numerous similarities[27]. At the same time, these countries continue to vary along many crucial parameters. The discussion about conversion or diversion among countries will also play a role in the next section that revisits some concerns about the VoC approach. They are essential for the comparative advantage that the US has to host the world's most vibrant biotechnology industry.

3.4 The Utility of the VoC Approach for the Analysis of the Biotechnology Industry

3.4.1 VoC vis-à-vis other Approaches

Many surveys inspired by VoC are comparative country studies[28]. By contrast, I will investigate the assumption formulated within the framework of VoC that LMEs have a comparative advantage in certain technological sectors, such as semiconductors, software development, and biotechnology, where flexibility and speed are pivotal for rapid wholesale innovation (Hall and Soskice 2001, p. 39). These propositions, however, have never been specifically tested for the case of biotechnology in the United States. The subsequent study will fill this gap. The reasons for the comparative superiority of America's biotechnology industry that was illustrated in the previous chapter will be investigated using the analytical framework suggested by the VoC approach. This approach, which will be elaborated further below, argues that such comparative advantage

[27] In that sense, focusing on the process of liberalizing capital restraints and market mechanisms, it may be appropriate to talk about 'liberalizing' rather than about 'neoliberalism' (Streeck and Thelen 2009).

is achieved when the political-economic setup of institutions in a country is complementary to the coordination needs of a specific industry.

Chapters 5 and 6 are dedicated to the most important institutional complementarities for the business of the biotechnology industry. Some of them, such as patenting and access to varied sources of capital, can indeed be derived from features that the VoC-typology ascribes to the United States as a liberal market economy. Yet other important factors crucial for the competitive advantage of the industry in the United States, particularly clustering on the sub-national level, will come to the fore too. They will reflect on the limits of the VoC approach, which for that reason, will be compared with other theoretical approaches used to analyze the biotechnology industry: towards that end, I will discuss studies on 'national systems of innovation' and concepts of clustering and embeddedness of firms.

3.4.2 VoC: What is it?

The approach to look at variations in capitalist societies that is used here was introduced by Hall and Soskice (2001). Influenced by the French Regulation School (Boyer 1990), which analyzed the movement away from mass production toward new, flexible production regimes, VoC brings the firm into the center of economic analysis. VoC takes a relational view on the firm, assuming that business actors interact in a strategic way, trying to pursue their individual interests under the circumstances of a given set of institutions. To flourish,

[28] See for instance Coates (2005), Hancké (2007). Equally important, the majority of these comparisons are empirically focused on European countries. The United States poses as the 'ideal' LME, but rather in theory than by empirical evidence.

a firm has to engage other actors in a number of spheres of the political economy: to raise finances (on capital markets); to determine working conditions and salaries (industrial relations); to safeguard that employees have an appropriate skill set (training and education); to get access to technologies and other inputs, but also to compete for market shares (inter-firm collaborations) (Hall and Gingerich 2009, p. 452). Hence, much of the work that firms carry out is relational to alleviate coordination problems and to mitigate transaction costs, both within and outside the firm.

In so doing, the approach links the competitiveness of the individual firm to an 'institutional comparative advantage' of national economies. Such 'comparative advantage' is assessed in terms of key complementarities that are provided by the institutions of the political economy of a country. It implies that nations with a specific set of coordination mechanism in one sphere of the economy are also likely to develop complementary practices in another sphere, too. For example, where there are dense business networks to sustain a joint vocational training program, the same networks may also be deployed for collective bargaining with employees (Hall and Soskice 2001, p. 18). Hence, institutional practices are not distributed randomly across nations, but their clustering allows for typifying capitalist economies.

Based on the way in which economic actors coordinate their endeavors and what kind of support a country's institutions of political economy provide for, VoC studies originally

distinguished between two types of capitalist economies[29]. On the one hand, there are liberal market economies (LME) such as the United States, Canada, Australia, and the UK, in which coordination among economic actors is considered to depend largely on the market, on contracts, and on other legal instruments. By contrast, in so-called coordinated market economies (CMEs), such as Germany, Sweden, or Japan, informal cooperation, deliberation, and sanctioning is more important for coordination among actors. Sometimes institutional support is provided for by the state directly, sometimes by corporatist organizations.

In the spheres of political economy mentioned above, firms in liberal market economies like the United States rely more extensively on market relations to resolve coordination challenges than it is the case in CMEs. Consequently, in these spheres LMEs can be characterized by institutional support structures for market-forms of coordination (Hall and Soskice 2001, pp. 27-31):

Financial systems and markets for corporate governance: Financing of firms is reliant on well-established and transparent equity markets, where dispersed investors value the company based on publicly available information. And while for new firms in high-technology fields venture capital often provides funding and guidance, corporate governance structures in LMEs are dominated by publicly traded firms whose current profitability is the most crucial dimension for performance, and reflected in the share price.

[29] Hall and Gingerich (2004) later also analyzed so-called 'hybrid systems', such as mixed market economies and (East European) 'Emerging Market Economies'.

Industrial relations: In absence of work councils and trade unions, firms in LMEs rely on individual bargaining between employers and employees. Competition in the labor market leads to a high level of fluidity, which is modulated by macroeconomic policies. In these markets hiring and firing of employees is easier than in CMEs, so that both employers and employees invest in general skills that are transferrable across companies.

Education and training: complementary to the fluid labor markets mentioned previously, companies are loath to invest in very specific training schemes as they fear that their trained staff would simply be poached by other firms. From the perspective of the employee, anticipating many shifting jobs makes it rational to acquire a general skill set that is transferrable between employments. This assumes a high level of general education in LMEs, and that firms encourage their employers to acquire marketable skills. This institutional setup will also leave some firms short of employees with highly specialized, company-specific skills.

Inter-company relations: LMEs have a high degree on standard market relationships based on enforceable formal contracts. Since firms are vulnerable to fluctuation in short-term profitability, they find it more difficult to make long-term commitments to providers of inputs as well as to customers. At the same time, particularly in the United States, rigorous antitrust regulation prevents companies from relational contracts, for instance for joint developments of technologies. Instead of research consortia, or inter-firm collaborations that are common in CMEs, companies in LMEs rely on the licensing or acquisition of innovations, mechanisms which make necessary an effective system of intellectual

property protection. Related to this and to the fluidity of the labor market, in LMEs technology transfer takes place through the movement of highly trained staff from one firm to another (or from research institution to private firm).

As a result of these specific institutional setups, liberal market economies have many institutional complementarities across the sub-spheres of the economy. For instance, flexible labor market arrangements allow companies to dispense with staff in an economic downturn and as a reaction to financial markets expecting the company remaining profitable. Similarly, educational arrangements in favor of general rather than specialized skills, are complementary with fluid labor markets. And, in the context of a legal system that inhibits relational contracting, licensing agreements are more effective than inter-firm collaborations for technology transfer (see Fig 1.4 Hall Soskice, 2001 p. 32).

VoC not only assumes that the different capitalist types have varied institutional support structures, but also, that this renders comparative advantage for certain types of industries and innovations in those countries. This approach postulates that CMEs dominate in sectors where staff and financiers' longer-term commitment allows for incremental improvements of production systems. By contrast, LMEs have a comparative advantage in high-tech sectors characterized by rapid innovative turnover, such as semiconductors, software development, and biotechnology.

3.4.3 VoC and Globalization

VoC also makes a number of assumptions about globalization that are important for my analysis of the biotechnology industry. Because comparative institutional advantages lead to specialization in either radical or incremental innovation, globalization is supposed to confirm rather than undermine comparative institutional advantages of nations. As explained earlier (see 3.2), in knowledge-based industries such as biotechnology, labor costs alone would not be reason enough to relocate to countries with lower wages. Instead, VoC's theory of comparative institutional advantage suggests that firms relocate activities abroad to profit from when they can expect that the institutional framework in political economies of another countries are more conducive to the tasks at hand (Hall and Soskice 2001, p. 57). For instance, American car companies have relocated to and profited from the incremental improvement of certain aspects of their manufacturing activities carried out in CMEs. Conversely, we can find such 'institutional arbitrage' in the behavior of pharmaceutical firms from Europe that move R&D activities to the United States (see 2.7 above), an LME whose institutional framework is more supportive of radical innovation.

Moreover, as a response to globalization it has been argued that in CMEs, strategic coalitions between employers and employees in some industries and advocate for deregulation in others. By contrast, in LMEs business actors are generally considered to be calling for deregulation (Hall and Soskice 2001, pp. 57-58). Looking at the various aspects of regulating biotechnologies, with regards to safety, patenting, and regulatory approval of drugs, a more complicated picture will arise (see 5.6-5.8 below). It has therefore been

argued that instead of the old varieties of capitalism, in reaction to globalization pressures, we witness

> *"the emergence of varieties of neoliberalism – of diversity within convergence, of the forging of different 'roads to globalization.'* (Cerny, Menz, and Soederberg 2005, p. 21)

Taking up from this argument, my study explains the road to globalization of America's capitalism and how it became – and to this date is - the variety of neoliberalism most attractive for the biotechnology industry.

3.4.4 Criticism of the VoC-Approach

The VoC-approach is being criticized on many accounts for various reasons: that its typology based on two different models of capitalist societies is reductionist; that it is ignorant of the role of the state; too static and ignorant of the role of conflicts; and too functionalist. Part of this criticism is owed to the fact that the proposed VoC-approach was meant to be a research agenda about, rather than a full-blown account of, the differences of capitalist societies. While it is not the purpose of my study to contribute to these discussions[30], I will address some of those criticisms that will later play a role for my analysis of the biotechnology industry.

[30] For an overview see Hancké (2007, pp. 6-7).

To begin with, not everything with a coordinated market economy, such as Germany, is organized according to non-legal, tacit agreements. Conversely, in the United States many aspects of economic life that may very well be of crucial importance for the biotechnology industry do not occur according to market principles and hierarchical, legal agreements. For instance, my study will look at business networks that link biotechnology firms with specific types of funding organizations (e.g. Venture Capital and Angel investors), which are not easily typified within the dichotomy of contractual (LME) or informal (CME) coordination. My study therefore wants to disentangle to what extent the particular variety of neoliberalism in the United States that seems to be so conducive for the creation of the world's most competitive biotechnology industry, can be characterized by parameters suggested by VoC, and to what extent other factors play a role.

Second, the strength of the VoC approach, to put the individual firm into the center of attention, is also its largest deficit, because there is no role for macroeconomic structures, in particular the state. Unlike other approaches to group capitalist countries according to the role of the state[31], it has also been argued that adding a separate variety of capitalism defined exclusively by the role that the state plays, adds little analytical value (Hancké, Rhodes, and Thatcher 2007, p. 15). My own approach for bringing the state back in therefore will based on empirical evidence from personal interviews with biotechnology actors. I will specifically focus on their strategic business decisions and see what type of state intervention (or lack thereof) created the specific support structures and institutional complementarities that made certain regions in the United States the world's most

[31] See for instance Amable (2003).

competitive locations for biotechnology. I will demonstrated that what VoC calls the 'comparative institutional advantage' of the United States was the result of politics and policies of a series of neoliberal political decisions to boost the United States competitiveness in advanced technologies in general and in biotechnology in particular.

Third, it has been contended that VoC is too static and cannot accommodate for the role of conflicts. But whereas VoC stresses the importance of business networks for coordination and strategic decision-making for firms in CMEs, they play an important role in LMEs too. The rise of the biotechnology industry's interest group representation into an influential lobbying organization, which will be discussed in conjunction with healthcare reform efforts (see 6.4 below) is a case in point. That episode will also demonstrate that the healthcare system in the United States is more than a support structure that economic actors passively take advantage of (a criticism of VoC). Instead, business actors also use business networks to wield political influence to bend the institutional support structure in their favor (in this case: Keep federal oversight over U.S. healthcare at bay).

Lastly, VoC has been also criticized for being focused on the functional outcome of coordination with little room for dysfunctionalities. By contrast, my study will also highlight the side effects and unintended consequences of the specific setup for coordination. A case in point will be the crucial role that the protection of intellectual property rights – a core tenet of neoliberal policies - play for the biotechnology industry. But whereas the United States have played a leading role in the extension of such rights, domestically the culture of patenting in biological sciences has caused an inhibition of

innovation. This negative unintended consequence of too many conflicting patent claims has been called a “tragedy of the anti-commons” (Heller and Eisenberg 1998) (see 7.4 below).

In addition to such debates within the VoC frame of reference, it is also worth looking at wholesale alternatives. Some, such as concepts of embeddedness and national innovation systems, have already been applied for studying the biotechnology industry, and they will therefore be discussed next.

3.5 Embeddedness of the Firm

According to Polanyi (1944), to embed economic activities in society, market mechanisms alone are not sufficient, but also required are mechanisms such as reciprocity and redistribution. By the 1980s, economic sociologists took this analytical perspective when looking at the interaction of the firms and their social context in which they operated. Starting point was the work of Mark Granovetter, who argued that

> *“the anonymous market of neoclassical models is virtually nonexistent in economic life...transactions of all kinds are rife with the social connections described...there is evidence all around us of the extent to which business relations are mixed up with social ones.”* (Granovetter 1985, p. 495).

Embeddedness of the firm, then, emphasizes the role of concrete personal relations and structures (such as networks) in creating trust and discouraging deceit. For handling complex and idiosyncratic transactions, the hierarchical structure of a vertically integrated firm that Chandler (1977) saw so superior, is not necessarily the single best answer. The pressure for vertical integration is higher when a company lacks the network of personal relations. Small firms that are embedded in a dense network of social relations that overlay their business relations can resist the pressure to become integrated into a larger firm (Granoveter, p. 507). Conversely, to become vertically integrated, certain requirements have to be met with regards to the level of market power, access to capital, and appropriate access to regulatory authorities, which is not always possible for a small firm. In the next chapter, these theoretical, organizational premises will be gauged against the empirical evidence of biotechnology companies' relationships. This will put a test on the typology of VoC, which assumes that in the United States as an LME, the level of formalized, contractual relationships is high for advanced technologies such as biotechnology.

Moreover, the theoretical assertions about embeddedness gave rise to a whole range of inquiries into the relationship between firms and their regional or local setting. Historically, the geographic concentrations of trades and companies in some industries date back for hundreds of years. Shipbuilding has always been an activity best carried out close to the water and iron and steel industries arose in close proximity to iron ore and coal. During the 20th century, certain regions became synonymous for certain products, such as Hollywood for movies and Detroit for cars. Intellectually, the importance of industrial location can be traced back to Alfred Marshall's *Principles of Economics* (Marshall 1891), which

established economic geography as a scientific field. The removal of the factor location from the radar of economic mainstream theories only occurred in the mid-20th century, as a result of the surge of neoclassical economics.

More recently, the question of location had its reincarnation in theories about clustering. In general, the phenomenon of clustering represents a particular combination of competition and cooperation. Clustering is path dependent and the origin and evolution of clusters is determined by local and historical circumstances. According to Michael Porter,

> *"[a] cluster is a form of a network that occurs within a geographic location, in which the proximity of firms and institutions ensures certain forms of commonality and increases the frequency and impact of interaction."* (Porter 1998, p. 226)

Changes in technology have not diminished the role that location used to play for competition. Location still matters, but different from an era in which economic development was based on the production of heavy industries. For example, whereas the early iron and steel industry had to locate close to iron ore and coal, industries that depend on the creation of advanced knowledge and technologies are assumed to be much more 'footloose' as they no longer locate close to raw materials. Such footloose industries rely on the highly specialized, institutions, services, and particularly the specific skills of highly trained individuals[32]. These professionals are high in demand, but they have high demands themselves: The 'creative class' of knowledge workers have high standards as

sophisticated customers, and they want the location in which they settle to be a pleasant and stimulating environment (Florida 2004, 2005). Paradoxically therefore, due to the concentration of these new resources, competitive advantage in a global economy often seems to be created and concentrated very locally[33].

Biotechnology has been characterized by a high degree of commercialization from its earliest stages (Kenney 1986). At the same time, biotechnology relies on public science more heavily than other industries (McMillan, Narin, and Deeds 2000). This is a contradiction not easily reconciled with VoC's predictions for advanced technologies profiting from market-based coordination mechanisms in LMEs. The cause for this is the centrality of knowledge in the biotechnology industry. Because in today's global competition knowledge has become a pivotal asset, its creation and dissemination has received ample attention both by theorists and policy makers. Michael Polanyi (1966) dubbed the term 'tacit knowledge' for all those things people know but cannot put into words, and cannot formulate as rules. Such knowledge, which is embodied in people and in institutions, tends to be difficult to transfer. The spill-over of tacit knowledge appears to be a function of the geographical proximity among the entities and clustering is a consequence of this. Clusters are sustained by research institutions, universities, and companies. As knowledge becomes the pivotal asset in economic transformations, regional knowledge capabilities should be rooted in 'open science' generated by publicly funded institutions, which is then being exploited by private firms (Cooke 2005, p. 1130).

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[32] Other works (e.g. Saxenian (1994) dwelled on the regional variations in firm embeddedness caused by cultural variation.

[33] See also the discussion on the global financial architecture above.

For a company, it is advantageous to locate some activities into such a conglomerate and to profit from the spillover of otherwise hard to transfer tacit knowledge. The idea of such spillover is that interaction and the exchange of information within a cluster is characterized by an unstructured, broad, and almost automatic ‘local buzz’ (Bathelt, Malmberg, and Maskell 2004).

On the other hand, Owen-Smith and Powell (2004) emphasize that innovative biotechnological knowledge is not only accessed through an open ‘local buzz’. Instead, actors also exchange new knowledge with other creators of new knowledge elsewhere through strategic partnerships. Such flows of knowledge along so-called ‘pipelines’ are more formalized than the tacit buzz. Only when knowledge can be codified and generalized is it possible to exchange knowledge beyond geographic proximity and to participate in networks of interregional and international reach. The United States, a rules-based, market-led LME, should have a comparative institutional advantage for such legalized, formal exchange. The relevance of open versus commodified sciences for the contemporary state of the industry should therefore be an important topic for biotechnology actors (see 4.6.1 below).

Looking at the relevance of tacit vis-à-vis formalized knowledge or the dynamic of clustering alone will not be sufficient to understanding the dynamics of the biotechnology industry for two reasons. First, as pointed out by Ibata-Arens, Dierkens, and Zorn (2006), the strength of the subnational focus of such approaches is also its weakness as it ignores the relevance of the common national policy prescriptions and political parameters. This is

also the omission of highly informative sociological studies that explicitly address the clustering of the United States biotechnology industry (Powell 1996; Powell et al. 2002; Powell, Koput, and Smith-Doerr 1996). And VoC, although looking at complementarities on the national level, is short of explanatory power, too. Instead, an historically and empirically informed reconstruction of the national political context – the so-called national innovation systems - will be suited better to look at how biotechnology clusters obtained their position.

Second, studies on clustering and tacit knowledge, like most innovation studies, including work inspired by VoC, highlight the supply-side and ignore the demand side (see also Carlsson (2006, p. 65)). This is a gap that, after turning to national innovation systems, also deserves further theoretical scrutiny.

3.6 National Innovation Systems

Derived from Friedrich List's concept of 'national systems of production' (List 1841), systemic approaches to innovation have drawn attention on the institutional structure that supports innovative activities within an individual country. Beginning in the late 1980s the concept of 'national systems of innovation' was developed by different authors. Taking Japan (Freeman 1987) and Scandinavian countries (Lundvall 1985) as first examples, the concept was subsequently refined through a series of comparative studies (Lundvall 1992, Nelson, 1993 #162). These authors have argued that it would be arbitrary to look at the innovation system of a nation independent from its overall economic system. Politics and

policies pertaining to innovation touch upon issues such as economic policies, education, or defense. Besides being responsible for a general macro-economic climate, government policies and programs that affect innovation could be either the general support for education and research or the specifically tailored programs for certain scientific endeavors, technologies, or companies. Path dependence partly intentionally, partly not, causes considerable continuities in a nation's innovation system (Nelson and Rosenberg 1993, p. 16), which can be defined as

> *"that set of distinct institutions which jointly and individually contribute to the development and diffusion of new technologies and which provides the framework within which governments form and implement policies to influence the innovation process. As such it is a system of interconnected institutions to create, store and transfer the knowledge, skills and artifacts, which define new technologies. The element of nationality follows not only from the domain of technology policy but also from elements of shared language and culture which bind the system together, and from the national focus of other policies, laws and regulations which condition the innovative environment."* (Metcalfe 1997, p. 289)

While a number of studies on national innovation systems have spelled out in detail the factors responsible for the development of the biotechnology industry in the United States, they are focused on this country as a 'Best Practice' model[34] for stimulating the supply-side of biotechnological innovation. An inclusion of the demand-side in concrete studies on the

[34] See for instance Giesecke (2001) and Pisano (2002).

biotechnology industry, coming from diverse perspectives, such as history (Bud 1998; Kenney 1986; Zucker, Darby, and Brewer 1998), political economy (Dolata 2003), or comparative studies (Barben 2007; Barben and Abels 2000; Gottweis 1998; Jasanoff 2005) is missing. This void is all the more surprising as innovation theories do acknowledge the importance of demand side (see for example Carlsson (2002)). It will therefore be addressed next.

3.7 Bringing in the Demand Side

For manufacturing industries, it has been long-established orthodox economic knowledge that expenditures on R&D correlate with the sales of an industry. Schmookler (1966) argued that the anticipated market for a product determines the amount of R&D dedicated towards improving a product or reducing its costs. The assumption, according to which all information about the demand for a product is engrained in its price, has subsequently been refined. For instance, market prices do not reflect how the demand-side is organized and what should be a publicly available product or service: Instead,

> *"What is 'public' depends in part on certain technological attributes of products and services and in part on what people think is important and valuable"(Nelson and Winter 1982, p. 368).* [35]

[35] Despite this analysis, Nelson's subsequent deliberations on national innovation systems are not taking into account the shape of the demand side (Nelson 1993).

Others have argued that in a global economy, it is the *quality* of local demand that matters, not its *size*. Consequently, clusters of linked industries can play a pivotal role in shaping the demand side (Porter 1998, p. 212-13). In a similar vein, Meyer-Krahmer and Reger (1999) postulated that transnational companies decide upon their foreign investments based upon the following criteria:

> *"Where are the attractive, future-oriented markets in which users can be learned from, and which generate a sufficiently high return-on-investment for costly product development? Where can these markets be best served by highly developed production, logistic and supply structures? Where would it therefore be worthwhile to build up value-added in one place? In what countries do attractive markets, highly developed production structures and excellent research conditions coincide, so that innovative core activities can be concentrated there?"* (ibid., pp. 770-1)

These factors played a role in the decisions of pharmaceutical companies to locate increasing part of their business to the United States, as already outlined in chapter 2 (see 2.7). Moreover, as the following chapters will illustrate, all the above factors are crucial for the clustering of biotechnology activities in specific regions in the United States.

More than other capitalist countries, in the United States public needs are increasingly provided for by commodified, privatized, goods and services. Health is a case in point, and healthcare in the United States is exceptional from all other wealthy industrialized nations in several ways: It is more expensive than in any other wealthy country (OECD 2007, p.

89). At the same time, America's health system is predominantly based on private insurance, and despite federal programs such as Medicare and Medicaid, there are still 14 percent of the population – some 48 million – without any coverage at all (ibid., p. 97). Because of these discrepancies, a wide range of health-related services and products, including drugs, are being withheld from a considerable share of the population (Oberlander et al. 2005; Morone and Jacobs 2005). Nonetheless, Americans account for the highest annual per-capita-spending on drugs - $792 - which was 86 percent above the OECD average (see OECD 2007, p. 93).

Innovation in healthcare technologies, including biotechnologies, is therefore more complicated than the theoretical equilibrium that gauges innovation dependent on consumers' evaluation. One cannot assume a linear development from science to technology and to meeting the needs of the demand side[36]. Although medical biotechnologies should ultimately benefit human patients, there are other and quite different aspects to the shape of the demand side, too. *First*, some biotechnologies are purchased by pharmaceutical companies, based on their strategies for developing new drugs. In these cases biotechnologies are only indirectly connected to the patients' demands. *Second*, there is a doctor, whose advice about which drugs benefit the patient best should be impartial with regards to benefitting himself. *Third*, the doctor's advice is only consequential if the drugs recommended are indeed accessible for the patient. Therefore, if the patient does not or cannot pay for medicines on his own, the institutional

[36] The complexity of healthcare provisions dovetails with the systemic approach by Edquist and Hommen (1999) who describe innovation as a non-linear chain link model. Yet they do so without addressing the dynamics of market forces.

setup of the health insurance system in place will be crucial for whether or not a patient's demand for a drug will be met.

As a result, there are partly alternative, partly competing modes of interaction between, for instance, producers of scientific knowledge and patients; between pharmaceutical companies and doctors; or between healthcare maintenance organizations (HMOs) and the government. None of these feedback loops have been sufficiently studied with regards to biotechnology innovation. Moreover, all of them acquire crucial coordination efforts of firms. I therefore argue that the complementarities of the provision of healthcare in a country and the comparative advantage that it provides for advanced health technologies, including biotechnologies, are crucial. The standard VoC approach, which postulates the complementarities between the United States' liberal market economy and biotechnology, should therefore be extended to the demand side for biotechnologies to explain the country's comparative advantage.

3.8 Conclusions and Outlook

The biotechnology industry, I argue, is an example for the intended, as well as the unintended consequences that neoliberal market-driven transformations bring about. Theories about creative destruction, variations among capitalist societies, the embeddedness of economic actors, and of national innovation systems, all bring to the fore useful aspects of the evolution of the biotechnology industry and the preeminent position of the United States in this endeavor. Yet this alone does not take account of the larger social

effect that biotechnology may also have. It may very well be that successful, competitive biotechnology companies become embedded within certain regions where they create localized benefits. It may also be that this adds to the comparative advantage that the United States has in attracting internationally competing industries, such as transnational pharmaceutical companies. From a neoliberal viewpoint, both theoretically and practically, this would be a successful outcome. At the same time, these economic activities may not only have the beneficial effects mentioned above, but also puts an extra strain on society at large, as they add to inequalities in healthcare.

I therefore argue to put the competitive advantage of the biotechnology industry in the United States into this broader context. Policy-makers continue to boast the supply-side successes that are the consequences of their neoliberal policies, while ignoring other consequences. Such myopia is similar to the initial enthusiasm about deregulating the financial industry and the comparative advantage that the United States – and particularly firms operating in the organizational and regulatory environment of Wall Street - enjoyed thanks to new innovative financial vehicles. Only when this finance-led economic bubble burst were these neoliberal, market-led policies being criticized. They were, however, a core component of the original neoliberal policy prescriptions of the American variety of neoliberal capitalism.

This also demonstrates the modified role of the state, which is not withering away, but is supposed to fulfill new tasks instead. The neoliberal state, while deliberately withdrawing from certain social duties, is proactive in promoting economic coordination and

competition. Domestically, this ‘leaner, meaner’ state is considered to provide a scientific-economic framework – higher education, supply and demand for advanced technologies, rules to govern economic actors and financial markets – which allows private actors to compete at the global level. Internationally, states compete with each other to provide a most favorable environment for these private actors.

Against this theoretical backdrop, I will analyze how the biotechnology industry was shaped by the evolution of neoliberal, supply-side-driven economic policies in the United States. The path dependence of certain key federal policies, related to military as well as other scientific research, shaped first the landscape of scientific excellence and second, the clustering of the fledgling biotechnology industry in the United States. Moreover, these interventions triggered competitive advantage and clustering to the effect that a few local biotechnology industry clusters in the United States have gained an overwhelming global competitive advantage.

Over time, biotechnology companies increasingly enjoyed competitively favorable terms in the United States from another crucial institution of the American political economy, the privatized, deregulated, healthcare system. In a similar vein, as the deregulation of America’s financial system provided the complementarities that made the country the world’s most competitive location for global finances (with all the consequences), America’s deregulated healthcare system is crucial for making the American variety of neoliberal capitalism so conducive for the biotechnology industry. My final analysis will therefore look at the intended and unintended consequences of the neoliberal American

biotechnology innovation regime. Yet the first step will be to look in the next chapter at the role of private corporate actors in this regime and discuss how biotechnology companies conduct their business.

Chapter 4: Creative Destruction and Institutional Support Structures

> *"Spectacular prizes much greater than would have been necessary to call forth the particular effort are thrown to a small majority of winners, thus propelling much more efficaciously than a more equal and more 'just' distribution would, the activity of that large majority of businessmen who receive in return very modest compensation or nothing or less than nothing, and yet do their utmost because they have the big prizes before their eyes and overrate their chances of doing equally well. Similarly, the threats are addressed to incompetence. But though the incompetent men and the obsolete methods are in fact eliminated, sometimes very promptly, sometimes with a lag, failure also threatens or actually overtakes many an able man, thus whipping up everyone, again much more efficaciously than a more equal and more 'just' system of penalties would."*
>
> Joseph A. Schumpeter: Capitalism, Socialism and Democracy (1942, pp. 73-4).

4.1 Introduction

In the past, the typical 'textbook development' (Kenney 1986) of a biotechnology company would have unfolded more or less as follows: a university professor who makes an invention decides to commercialize it outside of the university. While staying in academia, he sets up a company with the help of venture capital (VC). As the new corporation does not have any products, the venture capitalist takes shares in the company that will later on

be sold with considerable profit when the corporation is launched in an initial public offering (IPO) at the stock market. This chapter will explain how the world of today's biotechnology industry has grown more complex. Starting out with the relational view on the firm as postulated in the VoC-approach I will analyze how business actors try to pursue their individual interests under the circumstances of a given set of institutions throughout different spheres of political economy. Taking advantage of different parts of the institutional support system that surrounds them, biotechnology actors rationalize their behavior and make strategic business decisions. This way, looking at their business considerations will confirm the three claims made at the outset: The centrality of big pharma's drug development paradigm; the support infrastructure shaped by federal policies; and the crucial importance of the U.S. healthcare market.

As explained in the previous chapter (see 3.4.2), VoC postulates that liberal market economies like the United States provide a comparative institutional advantage for industries engaged in rapid innovation. LMEs rely more extensively on market relations to resolve coordination challenges than it is the case in CMEs. Consequently, in these spheres LMEs can be characterized by institutional support structures for market-forms of coordination (Hall and Soskice 2001, pp. 27-31). The empirical evidence from interviews with biotechnology actors will be addressed according to the following spheres of the economy:

1) Financial systems and markets for corporate governance: Financing of firms is reliant on well-established and transparent equity markets, where dispersed investors value the

company based on publicly available information. And while for new firms in high-technology fields venture capital often provides funding and guidance, corporate governance structures in LMEs are dominated by publicly traded firms whose current profitability is the most crucial dimension for performance, and reflected in the share price.

2) Industrial relations and education and training: As there is considerable overlap between these two spheres, they are addressed together. Against the backdrop of firms in LMEs relying on individual bargaining between employers and employees and competition in the labor market leading to a high level of fluidity, employees are hired and fired easily. Employees, anticipating many shifting jobs, acquire a high level of general skills that is transferrable between employments. And while firms encourage their employees to acquire marketable skills, this institutional setup will also leave some firms short of employees with highly specialized, company-specific skills.

3) Inter-company relations: LMEs have a high degree on standard market relationships based on enforceable formal contracts. Since firms are vulnerable to fluctuation in short-term profitability, they find it more difficult to make long-term commitments to providers of inputs as well as to customers. At the same time, particularly in the United States, rigorous antitrust regulation prevents companies from relational contracts, for instance for joint developments of technologies. Companies in LMEs rely on the licensing or acquisition of innovations, mechanisms which make necessary an effective system of intellectual property protection. Related to this and to the fluidity of the labor market, in

LMEs technology transfer takes place through the movement of highly trained staff from one firm to another (or from research institution to private firm).

After an overview of the companies sampled (4.2), the query is organized around how these economic spheres in the United States as a liberal market economy are structured and how biotechnology firms make their rational decisions based on the support from them: Financial systems and markets for corporate governance (4.3); Industrial relations and education and training (4.4); and Inter-company relations (4.5). As it will turn out, VoC is too unspecific for a complete understanding of the comparative advantage that the biotechnology industry in the United States enjoys vis-à-vis other nations. To begin with, it has to do with the nature of the industry at hand and that the reference industry for most biotechnology firms is the pharmaceutical industry. Drug development is an idiosyncratic process that does not comply with the notion of rapid innovation. Despite the high level of creative destruction, the development of new medicines remains a very long and unpredictable process in which a resilient, ‘old’ blockbuster drug business model continues to have the upper hand over other scientifically more promising, approaches. This is illustrated by a closer look on the genomics industry.

In addition, there is the nature of the institutional complementarities that are offered to biotechnology firms in the United States. In some spheres of the political economy the comparative advantage that biotechnology in this country enjoyed is due to the fact that there is more informal coordination (for instance in finance) than the model of a liberal market economy would assume. The consequence is that the biotechnology industry tends

to cluster informally around crucial support structures, such as research institutions, human resources, and capital (4.6). In fact, the clustering of the biotechnology industry can only be explained because of the relevance of such informal coordination. In other spheres of the political economy, for instance the direct funding for R&D (4.7), biotechnology takes much more advantage of formalized, state-created coordination structures. Interviews will highlight those, but also the crucial role of state interventions with regards to the regulation of drugs and the healthcare system (4.8). The chapter concludes by outlining those dimension of the United States as a liberal market economy that the VoC approach could not account for (4.9). These will be further investigated in their historical context in chapters 5 and 6.

4.2 Overview of Sampled Companies and Results

Before discussing the substantive issues that seem to be prominently motivating the industry and its actors, a brief quantitative description of the companies included in this survey will be presented. Overall, more than half of all surveyed biotechnology firms were engaged in drug discovery and biomedical research. This group was dominant in all five regions, except for in Maryland, where they were they matched by biomedical device firms (Table 4.1).

Table 4.1: Types of Biotechnology Companies Surveyed

Company Type	TOTAL	NY	MA	MD	SF	SD	TOTAL %	NY %	MA %	MD %	SF %	SD %
Biomed/Drug Discovery*	75	15	18	10	13	19	52.4	50.0	54.5	40.0	52.0	63.3
Diagnostics	13	1	1	3	5	3	9.1	3.3	3.0	12.0	20.0	10.0
Biomed. Devices	14	3	4	2	2	3	9.8	20.0	12.1	8.0	8.0	10.0
Contract Research/Services	26	7	4	10	2	3	18.2	13.3	12.1	40.0	8.0	10.0
Pharmaceutical Company	7	2	4	0	0	1	4.9	6.7	12.1	0.0	0.0	3.3
Environment/ Agbio	8	2	2	0	3	1	5.6	6.7	6.1	0.0	12.0	3.3
SUM	**143**	**30.0**	**33.0**	**25.0**	**25.0**	**30.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

*inc. genomics

Biotechnology is a relatively new industry so that the majority of companies surveyed were less than 10 years old (Table 4.2).

Table 4.2: Age of Biotechnology Companies Surveyed

Age	NY	MA	MD	SF	SD	TOTAL	NY %	MA %	MD %	SF %	SD %	TOTAL %
1 -5	10	6	9	7	10	42	33.3	18.2	36.0	28.0	33.3	29.4
6 - 10	8	15	7	9	13	52	26.7	45.5	28.0	36.0	43.3	36.4
11-15	6	8	3	4	6	27	20.0	24.2	12.0	16.0	20.0	18.9
16 -20	2	4	3	5	1	15	6.7	12.1	12.0	20.0	3.3	10.5
> 20	4	0	3	0	0	7	13.3	0.0	12.0	0.0	0.0	4.9
average age:	14	10	9	10		**10.2**						
still existing 2 years later	22	25	18	20	19	104	73.3	75.8	72.0	80	63.3	**72.7**
not existing 2 years later	8	8	7	5	11	39	26.7	24.2	28.0	20	36.7	**27.3**

They were also relatively small companies with the majority of them having less than 100 employees and (excluding two outliers - a multinational pharmaceutical corporation and a transnational CRO, each with several thousand employees) an average staff of 94 (Table 4.3).

Table 4.3: Company Size

Employees	**NY**	**MA**	**MD**	**SF**	**SD**	**AVGE**	**NY %**	**MA %**	**MD %**	**SF %**	**SD %**	**AVGE %**
10 or less	7	2	4	4	2		23.3	6.1	16.0	16.0	6.7	13.6
11 to 50	14	12	15	7	11		46.7	36.4	60.0	28.0	36.7	41.5
51 to 100	5	10	1	7	5		16.7	30.3	4.0	28.0	16.7	19.1
101 to 200	1	4	4	2	7		3.3	12.1	16.0	8.0	23.3	12.6
> 200	3	5	1	5	5		10.0	15.2	4.0	20.0	16.7	13.2
average empl.	162*	276*	53	115.0	117.0							
average empl.	47**	139**	53	115.0	117.0	**94.2**						

* Including outlier companies (NY 26 and MA 33)

**Excluding outlier companies (NY 26 and MA 33)

4.3 Indicators of Finances and Corporate Governance

In LMEs, the predominant type of corporate governance is the firm that is publicly traded on equity markets. The value of these companies' shares is a transparent reflection of current profitability. Biotechnology firms do not easily fit into this pattern. As for the ownership of the corporations, two characteristics are noteworthy. First, a large majority (85 percent) was operating as an independent entity, whereas subsidiaries of US and

foreign companies constituted 9 and 6 percent, respectively. Second, with the exception of Massachusetts and San Francisco, a majority of companies was not yet traded publicly on the stock market, but held privately (Table 4.4).

Table 4.4: Ownership

Ownership (Percent)	NY	MA	MD	SF	SD	AVGE
Independent	83.3	75.8	92.0	88.0	86.7	85.2
subsidiary of US company	13.3	13.3	8.0	0.0	10.0	8.9
subsidiary of foreign company	3.3	13.3	0.0	12.0	3.3	6.4
Private	60.0	39.4	72.0	48.0	60.0	55.9
Public	40.0	57.6	28.0	52.0	40.0	43.5

Moreover, as biotechnology firms were spending half of their operational expenses on R&D, profitability was normally nowhere within reach. Instead, 77 percent of companies surveyed were making losses (Table 4.5).

Table 4.5: Profitability and R&D Expenditures

Cash Flow	MD	NY	MA	SD	SF	AVGE
profitable:	29.2	23.3	18.0	23.3	16.7	23.5
Loss	70.8	76.7	82.0	76.7	83.3	76.5
R&D as % of operational costs	46.3	50.8	61.2	68.6	50.9	56.7

The different approach towards finance is reflected by the fact that biotechnology managers seem to worry much less about profitability as about the ‘burn rate’, the velocity at which a company diminishes its financial assets. A typical drug development company would

'burn' money at a rate of at least $5 million per year[37]. Drug development is costly and companies are expected to move along as quickly as possible towards the clinical trial phase. These clinical trials to obtain regulatory and hence market approval by the FDA require even larger financial stamina and the annual 'burn rate' regularly would go up to $15-20 million. For a company with several drug candidates in clinical trials, annual losses could easily reach $100 million.

4.3.1 Venture Capital as a Source of Financing

In light of these stakes, the institutional support that biotechnology firms look for normally does not come from public resources or from conventional banks with loans. Instead, 69 percent of companies relied on those sources of capital – venture capital and angel investors - that were willing to take on the extra risk (Table 4.6).

Table 4.6: Source of Finances

Source	NY	MA	MD	SF	SD	AVGE
Angel investors	10.0	12.5	20.0	24.0	20.0	17.3
local VC	3.3	3.1	16.0	48.0	26.7	19.4
total VC	33.3	50.0	36.0	76.0	63.3	51.7

This financing structure is revealing as it exceeds the contractual market mechanisms postulated by VoC for the LME of the United States. Why do companies conceive of VC as an attractive source of financing? In terms of coordination efforts, many biotechnology

[37] Venture Capitalists, while using the same terminology, measure the 'burn rate' more narrowly by the month.

companies saw venture financing as a good way to obtain money with limited bureaucratic efforts. How this worked was exemplified by a biomedical device company that developed a hand-held blood glucose monitor for people with diabetes:

> *"Getting VC is no problem, because the founder of the company is known to the VC scene, and diabetes presents a huge market."* (Interview MD 19)

This quote highlights two important criteria for VC funding in absence of tangible products. First, personal, non-market relationships with investors is helpful. This aspect will be elaborated further when I talk about the logic of clustering, specifically the proximity between biotechnology firms and sources of finance, such as VC and angel investors (see below). Second, from the view of the investor, entering a potentially rewarding market is more relevant than current profitability. In general technological innovation financed by VC is an extrapolation. Instead of current supply and demand for a specific product, it is based on future expectations for markets, earnings and profits. In this sense, it is like other financial derivatives, such as stock options, bonds, or futures. The absence of tangible products is also the reason why intellectual property claims are of such importance. They become the bargaining chips (or in today's finance-dominated language: securitization of assets) for the innovators and the providers of capital.

This mechanism of financing is prone to a considerable degree of volatility. For instance, when VC funding doubled from 1999 to 2000, which was fuelled by the dotcom boom around internet companies, biotechnology firms profited too. But when many of these

investors lost their money as the speculative internet bubble deflated by the early 2000s, even solid biotechnology firms suffered from the receding availability of VC funds. The VC industry continued to appreciate investing in biotechnology companies and, for a while, the sector bounced back. Not only has venture funding for biotechnology gone up to unprecedented levels in absolute terms, but biotechnology also attracts a relatively larger share of the overall VC (Table 4.7).

Table 4.7: VC Funding for Biotechnology

Year	Total VC (million $)	VC for Biotech (million $)	Biotech Share of Total VC (%)
1995	7,996.00	829.00	10.4
1996	11,265.00	1,185.00	10.5
1997	14,871.00	1,414.00	9.5
1998	21,079.00	1,584.00	7.5
1999	54,048.00	2,104.00	3.9
2000	104,768.00	4,250.00	4.1
2001	40,577.00	3,473.00	8.6
2002	22,010.00	3,237.00	14.7
2003	19,777.00	3,672.00	18.6
2004	22,468.00	4,267.00	19.0
2005	23,173.00	3,916.00	16.9
2006	26,741.00	4,594.00	17.2
2007	30,886.00	5,239.00	17.0
2008	28,298.00	4,500.00	15.9

Source: National Venture Capital Association

Interviewed VC industry representatives indicated that, as a consequence of the internet boom and bust, there is a trend in the VC community away from ‘dabbling in biotech’. Instead, there are fewer, more specialized, and larger funds managing investments of up to several hundred million dollars. To spread the risk, VC firms initially invests only $1 to 7 million in one particular company, preferably with other VC firms until the whole VC financing builds up to $12 to 15 million. In exchange for their investment, VC firms

request a share of the company, usually about 50 percent. As VC funds have a finite life cycle, typically ten to twelve years, VC firms generally pursue one of the two exit strategies to recoup their upfront investment and a profit: Either by selling the stakes in the company, which normally generates a lower return on investment (ROI). Or through an Initial Public Offering (IPO), which is the more profitable alternative. At the same time, the chances of IPOs depend upon the general economic climate and whether stock markets are conducive to it.[38]

In general, only one in six companies ever goes public and one in three is acquired. As VC firms aim at an ROI of 15 to 20 percent annually, such high returns can only be achieved when the inevitable attrition – creative destruction – of companies is carefully managed. A most profitable allocation of resources cannot be achieved within one company alone, but only for a fund as a whole. Biotechnology corporate executives repeatedly complained about the short-sightedness of VC executives who were pulling the plug out of good companies. But from the viewpoint of the VC this is just the necessary spark for of capitalism's perennial gale of creative destruction. Company closures and mergers can be ordered at the discretion of the VC fund and may be necessary to keep the losses limited. The *ultima ratio* for the venture capitalist, in other words, is to compensate for the inevitable losers by nurturing a few companies into big winners.

[38] For example, in 1999, the year of the dot.com boom, there were 477 IPOs, 270 of which were backed by VC. In 2007, these numbers had declined to 155 and 86, respectively (Thomson Financial 2008, p.39).

Especially for the smaller and younger start-up companies interviewed, many of which were previously receiving small-scale public funding, attracting VC was considered a sign of maturation. VC firms not only provide money, but as part of the nurturing environment that they want to create for their investment they also help with managerial issues. VC firms tend to dominate the corporation's governance by nominating the majority of the Boards of Directors. They can assist the management in creating and implementing their business and product development strategies, as well as in recruiting key executives and in undertaking additional financing initiatives, such as arranging corporate partnerships. In VoC terminology, venture capital is an effective tool for the coordination problem with regards to where and how to invest money into innovative activites, while also keeping a close grip on the performance of the investment. It is part of the conflicting business rationales and strategies, that the interests of biotechnology firms obtaining VC and the VC firms handing it out are not always congruent.

4.4 Industrial Relations and Education and Training

VOC postulates that the comparative institutional advantage of LMEs in high-tech industries is based on the fact that the interest of employers and highly skilled employees tend to coalesce, and that they have less need for a well-regulated framework for bargaining between capital and labor (Hancké, Rhodes, and Thatcher 2007, p. 20). A comprehensive investigation of the role of organized labor in high-tech industries is missing. To the best of my knowledge, the reason for this is that unlike in creative industries such as entertainment, the interest organization of highly educated, high-paid

employees in high-tech sectors is almost non-existent. Indeed, in interviews conducted with the biotechnology industry there was hardly a distinction to be made between owners of companies and employees. The distinction between owner and employee of a company is all the more fluid as, particularly for senior management, shares in the company by which they were employed represented a considerable part of the remuneration package.

Likewise, the salaries of employees in the biotechnology industry tend to be higher than in most other U.S. industries. In 2006, they earned $70,959 nationally, on average. While being lower than average salaries in the pharmaceutical industry ($ 86,892) and in information technologies ($ 76,257), the earnings of biotechnology industry employees were nearly $29,000 more than wages in the overall U.S. private sector (Battelle 2008).

The remuneration structure reflects the high level of formal education. Although VoC assumes that companies in LMEs due to the fluid labor market would be in need of 'generalists', the bar is considerable higher for people in the biotechnology industry: In the case of the companies surveyed, only 13 percent of employees were without a college degree, whereas 45 percent had a masters or doctoral degree (Table 4.8).

Table 4.8 Educational Level

Education Level Employees (Percent)	**NY**	**MA**	**MD**	**SF**	**SD**	**AVGE**
PhD	26.4	29.8	25.3	21.0	32.4	27.0
MSc	20.4	17.6	18.2	15.6	16.8	17.7
BSc	42.0	42.1	44.8	46.2	38.7	42.8
Highschool/None	12.3	10.6	11.7	17.2	12.1	12.8

This high level of academic, formalized training was a reflection of the fact that almost half the employees of the companies interviewed were engaged in R&D, which is more training-intense than other tasks such as production or marketing:

Table 4.9 Employees per Tasks

Tasks (%)	NY	MA	MD	SF	SD	AVGE
Management	16.0	12.6	16.8	13.8	11.6	14.2
Administration	10.0	15.2	9.5	16.3	11.2	12.4
R&D	43.0	47.9	42.6	42.3	56.6	46.5
Production	14.0	12.2	11.7	9.8	11.5	11.8
Sales	2.0	2.4	5.6	11.2	2.1	4.7
Others	15.0	9.7	13.8	6.6	7.0	10.4

Equally important, despite the high educational level, companies provided a range of different opportunities for their staff to continue their training. Almost all companies conducted some kind of in-house training, although not of the level of intensity that is known for instance from vocational training programs in companies in CMEs such as Germany. A high percentage of firms would offer tuition reimbursement to employees as incentive to attend classes at a college or university. An expression of the dynamism and the fluidity of the biotechnology industry labor market was the considerable turnover of staff leaving to obtain a higher degree. Moreover, in absence of inter-firm agreements to invest in training of human resources, in LMEs firms are encouraged to poach each others' most qualified employees. Further below I will explain that this is indeed the case, which is one of the reasons for cluster-building of biotechnological innovation (Table 4.10).

Table 4.10: Companies Providing Training (%)

Types of Training	NY	MD	MA	SF	SD	AVGE
Staff Leave for Higher Degree	30.0	39.4	28.0	40	36.7	34.8
Tuition Reimbursement	10.0	72.7	60.0	32	40.0	42.9
External	60.0	78.8	76.0	52	80.0	69.4
Internal	100.0	93.9	76.0	84	86.7	88.1

4.5 Inter-Company Relations

The United States as a liberal market economy should have a comparative advantage for biotechnology firms due to the institutionalized support structure for market-based relationships between economic actors. In LMEs, it is postulated, firms coordinate their business predominantly through enforceable formal contracts. But as they are measured in terms of short-term profitability, the long-term commitments are harder to come by. Likewise, due to antitrust regulation, particularly in the United States, inter-firm collaborations for joint technology development are less common than licensing agreements and acquisition of innovation. In looking at how firms deal with these challenges, various business models of biotechnology firms will come to the fore. Whereas the most competitive and potentially most rewarding segment was the development of drugs (in which half of all surveyed companies took part), other firms were hedging their bets on less risky grounds. Yet it became apparent that the financial muscles of large pharmaceutical companies continued to dominate the value-added chain of drug development. Along this chain, coordination has become more complex due to the variety of actors and business models. The new more networked R&D setup, still has large pharmaceutical companies occupying the commanding and coordinating heights, whereas biotechnology firms play an important, albeit not the only role, in the new division of labor.

4.5.1. Drug Development Hight-Tech Gamble

This segment of the biotechnology industry was characterized by the general spirit of a highly risky high-tech race to the market, with a potentially high reward. 'Creative destruction', a certain level of attrition is being taken for granted by both the providers of money and by the people who work in the industry. One quantifiable aspect of this was that two years after the interviews, 27 percent of the companies surveyed were no longer in existence (Table 4.11).

Table 4.11: Defunct Companies After 2 Years Per Company Type

Total	Drug Development	Diagnostic	Biomedical Device	Contract Research	Pharmaceutical	Environmental/ Agbio
27%	35%	23%	21%	15%	29%	0%

This high turnover rate can be a sign of companies' failure, but also the opposite. Many managers openly stated that being taken over by a larger entity is a desirable outcome:

> *"If there is independent technology development, the most attractive way of growing a company is going public. But there is no way to prevent a company takeover. Quite the contrary, success makes it even more likely."* (Interview SF 18)

The turnover rate was facilitated by the liberal, market-based, support structures of the United States. Companies are built, bought, sold, and dismantled according to short-term strategic needs. The high dynamism of the biotechnology industry is reflected particularly well by companies that are engaged in the development of new drugs. Two years after the

interviews, more than one third of the companies surveyed did no longer exist. Included in this survey were also 15 genomics firms - representing 20 percent of all firms engaged in biomedical and drug discovery research[39]. They formed a particularly noteworthy subset in this survey. As no other segment of the biotechnology industry, genomics firms are the embodiment of capitalism's creative destruction and dynamism. And, as explained in chapter 2 (see section 2.6 above) the rise of the genomics industry was a counter-factual case in point that in LMEs the value of corporations is a transparent measurement of current economic performance. Rather, the business of genomics companies rested on a technological potential that became extrapolated into a huge market validation so that adding value towards a prospective product becomes more important than current profitability. For a while, it even looked as if this industry may turn the table in the power relations of the pharmaceutical business. But when the scientific promises of the industry did not measure up to economic expectations, in the end the blockbuster drug model of Big Pharma prevailed.

A few of the genomics companies included in the survey will be scrutinized in detail as they reveal much about the boom and the bust of a new technology. I will begin with a success story of one rapidly expanding Massachusetts-based, genomics company: It was founded in 1993 by a VC person who attracted two scientists from the Massachusetts Institute of Technologies and from Albert Einstein College of Medicine in New York. The company developed genomics technologies for drugs against inflammatory diseases, cancer, and metabolic diseases such as obesity and diabetes, all of which were supposed to

[39] Two years after the interviews, 6 companies (40 percent of the sample) were defunct.

be launched in the United States first. However, a decade into its existence, the company did not have any commercial product, despite having spent $1 billion on research. In fact, the company had ten products in clinical trials, but was still at least two years away from market approval. Serious financial backing continued to come in from 20 strategic alliances with pharmaceutical and biotechnology companies. These R&D and licensing agreements were worth some $1.8 billion. Endowed with such deep pockets, the genomics company started to 'buy its way up' and acquired other entities that had experience in drug development and marketing to become a fully integrated drug company.

Yet also for this successful genomics company, translating genetic information into disease mechanisms, drug targets and lead substances, all of which are more value-adding in the logic of drug development, turned out to be much more complicated than initially expected. After being a benefactor, the firm ultimately became a victim of the perennial gale of creative destruction and ultimately ceased to exist. In May 2008, it was acquired by a Japanese pharmaceutical company that paid almost $9 billion to get a foot into the market for cancer drugs in the United States. And while this was still less than a third of what the company's shares were worth during the heydays of the genomics boom in 2000, at the time of the takeover the Japanese drug multinational paid a 53 percent premium for the publicly traded shares.

Others firms were less lucky. As in every case of speculative overvaluation, those who came late into the game were most likely to get burned first. This was the case with one Maryland-based firm that was started in 2000 by a group of Wharton MBA's in the hope to

exploit commercially patents on human genetic information. When it became clear that there are less genes and a smaller market for genetic information, the company changed business model towards drug discovery and screening technology in 2001. For this, it deliberately targeted a receptor that is responsible for the efficacy of 50 percent of all drugs, and 30 percent of top selling drugs such as those against cardiovascular diseases. At the time of the interview in 2002 the company had just laid off 40 percent of its staff, but that could not prevent its closure a year later.

Another genomics corporation was able to raise $90 million in an IPO during the days of the stock market's enthusiasm for genomics in 2000. However, already two years later the company was running out of finances and was at the brink of closure because, as a manager said,

> "*some deals got cancelled at a very late stage because Big Pharma had already overspent on genomics.*" (Interview MD 17)

Companies that were successfully managing the genomics downturn could no longer assume indefinite support from a big spender but had to get by with less as investors became more scrutinizing and staged their payments more cautiously (Interview MD 25). In 2004, at the deepest point of the depression of genomic companies, the market value of companies was sometimes less than the money they had in the bank. One company interviewed (SF 23) acquired a competitor just for that cash.

Not only genomics firms, in general the majority of biotechnology companies engaged in drug development indicated that they ultimately depended on a big pharmaceutical corporation. Often the biotechnology company provided a technology (e.g. a technology platform, a lead for a drug, or an early-stage drug candidate) and received milestone payments for moving that technology up the value-added chain. In general, the closer to market approval, the higher the stakes become and royalty and milestone payments can at times reach tens of millions of dollars annually. Considerable amounts of capital are being invested – and destroyed – particularly in the course of clinical trials. Biotechnology companies with several drug candidates in clinical trials easily lost $100 million annually. Sometimes, the destruction of capital went on for an amazingly long period, as one surveyed company accumulated $80 million in debts over a period of 20 years. Another surveyed loss-making company was ultimately taken over by a larger biotechnology corporation to co-develop a drug. But despite the staggering amount of $1.3 billion for which the loss-making company was acquired, the company continued to 'burn money' (Interview MA 21). Obviously, for biotechnology companies to stay afloat during the long and unpredictable process of drugs to the market requires the deep pockets of pharmaceutical firms.

A somewhat different approach was pursued by those few biotechnology companies that wanted to become a full-fledged pharmaceutical company on their own. Most times, they relied on a continuous substantial cash flow from drugs already marketed. One Massachusetts firm surveyed (MA 16) exemplified what it took to coordinate successfully the various ingredients for a high-risk-high-reward gamble in drug development. Founded

by a New York professor and a Wall Street investor, the company raised $20 million in VC. Investors, enticed by the company's strategic intellectual property portfolio of 80 patents issued in the United States and another 150 pending, rendered the IPO and a second offering worth $130 million. This money allowed acquiring a company whose product had already been marketed in Europe. Revenues and technologies were then used for a bootstrap strategy: First, obtaining regulatory approval also in the United States for the product already marketed in Europe. Second, using the revenues from the U.S. market to develop technologies further and becoming a full-fledged pharmaceutical company. Part of this strategy is an institutional arbitrage between healthcare markets, which will be revisited further below (see 6.2).

In their race to the market, companies that compete in a similar field of technologies watch each other closely. The company that is able to raise the largest amount of money will be the fastest to propel its technology further towards a marketable product, or, in the words of one participant

> "*Money buys you time. More money buys you more time."* (Interview NY 27)

Clearly, an institutional environment that allows time and money being so easily transferred into one another, is advantageous for industries with rapid innovative turnover. At the same time the biotechnology industry heavily depends on patenting. Patents – the core of LMEs instruments to regulate market-based exchange in biotechnologies – play an ambivalent role in 'rapid innovation'.

Critical patents may block certain technological trajectories for competitors which then may have to invent around these intellectual property barriers. And although companies saw this as a nuisance at some times, they also profited from it at others and accept this as parts of the rules that are laid down:

> "*We spend a considerable amount of our time and energy here to invent around other people's patents. But that's life*." (Interview MA 1)

As a rule of thumb, the faster the pace of innovation and the less tangible, the more arduous the protection of intellectual property turns out to be for the innovation process as a whole. The genomics industry was a case in point (see 2.6).

On the other hand, patents allowed for a variety of business models that would otherwise not have been possible: For example, one publicly traded drug development company (SD 4) had filed several hundred patent applications on its platform technology, which was supposed to be used in the development of drugs against obesity, psychic disorder, heart failure, and inflammatory diseases. These huge prospective markets in the United States and other industrialized countries made it possible for the company, while continuously losing more than $25 million per year, to raise over $320 million in VC and from the stock market.

Somewhat similar was the case of another drug development company surveyed (MA 23), whose business model rested on two pillars: First, a focus on the affluent, western, and

potentially highly profitable market for drugs against male erectile dysfunction and heart failure; Second a large portfolio of patents as the company had filed 240 patents globally and was issued 42 in the United States alone. The purpose of this so-called 'Me-Too-Drug' company was to improve or invent around proprietary versions of already existing drugs. Towards this end, the company received funding from a number of large pharmaceutical corporations. The rationale of these large pharmaceutical players was to check potential competitors, as all stakeholders in the drug development company would obtain the rights to co-marketing in the United States.

4.5.2 Biotech Laying Low: Reduced Risk, Alternative Routes, Lower Profits

Whereas the high-tech-high reward business model was dominant, it was not the only one that rational business actors in the biotechnology industry pursued. Since the road towards FDA drug approval is long, costly, and risky, corporate actors deploy various business models to hedge against the risk of all-or-nothing. This also leads to specializations along the value-added chain. At the lowest rank of the ladder were those companies that keep scientific research and technological development afloat. Servicing the most innovative firms, they provide the nuts and bolts of biotechnological innovation, products such as reagents, biological markers and testing animals, as well as services such as biomedical data management. It may not have been sheer coincidence therefore that two biotechnology managers in California, whose companies provide research tools for the biomedical research community, referred to the state's gold rush history when justifying their current business model:

"*We are selling picks and shovels to the miners.*" (Interview SF 7)

"There are a lot of gold diggers out here; we want to provide the shovels." (Interview SD 8)

As these corporations deliver real products, they were generally profitable. While some firms were complacent with the niche that they had carved out for themselves, there were also those servicing companies that wanted to reinvest their revenues to climb up higher on the ladder of added value and, for instance, carry out research for discovering drug targets. Such 'bootstrap strategy' for growing a company based on revenues may take longer, but has the advantage of maintaining independent from investors' requests.

One other company (SF 10) that decided against engaging into the risky business of drug discovery instead focused on technologies of how drugs are delivered in the human body. This biotechnology firm worked with already approved drugs, improved their delivery mechanisms then sold them back to a pharmaceutical company. Somewhat similar is the approach of a company (SF 15) that licensed the technologies from different companies to produce interferon. By selling interferon medicines in the United States and generating revenues, the company financed research on interferon-based medicines for new indications, which then have to clear the regulatory hurdle. Using an already approved drug and finding a new disease for it to cure is a common, cost-saving practice throughout the pharmaceutical industry[40]. It is particularly attractive for monoclonal antibodies such as interferon. These and other biologics are incomparably larger and more complex than the

chemical molecules many regular drugs are based upon and, consequently harder to synthesize. Hence, for biologics, finding a new disease for a known drug rather than finding a new drug for a known disease is even more appealing than for chemically derived drugs.

Despite these different business models service companies were in general more profitable than companies gauged by the potential of their technologies for a speculatively hugely profitable product in the future. By the same token, revenue-based service businesses are never traded for the huge amounts of money that the latter often muster.

4.5.3 Middle Grounds: From Diagnostics to Agricultural Biotechnology

About one fifth of all biotechnology companies surveyed were engaged in activities related to biomedical devices and diagnostics. Also here a majority indicated the overwhelming relevance of the Unites States healthcare market for the destiny of their business. The biggest difference to the drug development business model was the lower regulatory hurdle, which did not include clinical trials over several years with hundreds of participants. Hence, it was easier for a company to come to the market with for instance a diagnostics kit than with a new drug. In this sense, financial burdens and risks were somewhat mitigated, which is also reflected by the fact that two years after the interviews only a fifth of them had ceased to exist vis-à-vis 35 percent of all drug development companies (see Table 4.11).

[40]For the numerous side effects of this practice, which will be further elaborated in the concluding Chapter 7,

However, where exactly a company found itself on the spectrum between risks and rewards often times depended on the level of sophistication of its technologies and the potential volume of the targeted disease market. For example, one genetic test-chip company (SD 10) pursued a business model similar to many of the drug development companies surveyed: Aiming at diseases prevalent in affluent societies; a high-tech approach; strong patent portfolio; high speculative profit expectations; and trust of the investment community. This diagnostics company developed gene-based diagnostic tests for conditions such as cystic fibrosis and Alzheimer disease. Its IPR portfolio consisted of some 50 patents issued and another 150 pending worldwide. Because its founder was known as a successful entrepreneur to the biotechnology community and investors, the company's IPO raised some $270 million. Despite revenues of ten million dollars, the company still lost $36 million per year and the strategic exit scenario therefore was to be taken over by a big diagnostics company.

The majority of companies engaged in diagnostics or biomedical devices, even if they were predominantly conducting R&D and their products had not yet obtained market approval, had some production facilities. They were different from drug development companies in the sense that the logics of organizing production are different from organizing R&D. For example, whereas pharmaceutical production is often contracted out to low-cost locations and countries, the production of biomedical or diagnostics devices was kept closer to home. One company (SD 4), which developed a medical device to rescue heart stroke patients, insisted to stay in SD. Once the company would reach US market approval that would

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see also Angell (2009).

make large-scale production necessary, the company may consider outsourcing production, but it would favor a production company in the San Diego area. Similar arguments were made by a much more established, profitable diagnostics kit company with a staff of 500:

> *"The company will stay in San Diego, even if production will be extended: biologics is high-tech production and the standards are not easily met in cheaper regions or countries."* [Interview SD 23]

What this also shows is that despite the alleged strength that LMEs provide due to a flexible and not specialized labor market, these applications of biotechnologies cannot be shifted around too easily, but are bound to regions with the appropriate skill set. In sum, therefore, while the incentives provided by America's profitable healthcare market are similar to those biotechnology actors engaged in the high-tech-high-reward gamble of drug development, due to the more tangible nature of their dealings, biomedical and diagnostics companies hedge their bets differently.

Companies that were engaged in environmental and agricultural biotechnology were only a small sub-group (n=8) in this survey. Interestingly, two companies had started out delivering goods and services for agricultural purposes and later moved over to the biomedical field.

> *"We were initially a company for agbio/environment enzyme production. But then, we moved over to producing research reagents for biopharmaceutical companies, because of the better prospects for that market."* (Interview MD 14)

Conversely, there was not a single company that made the opposite transition from pharmaceutical towards agricultural biotechnology. Operating in different spheres in terms of profit expectations also affected agricultural companies in a very concrete manner when it came to choosing a location for their business:

> *"The problem with an agbio company in a cluster like the Bay Area is that we also have to compete with pharma/biotechn's higher salaries and business expenses here."* (Interview SF 19)

In this last regard, results would have been different in a biotechnology cluster, for instance around Durham in North Carolina, which has more agricultural biotechnology companies. As it stands, however, the findings corroborate this study's first claim: That the viability and dynamism of the biotechnology industry is driven by applications of biotechnology for medical purposes. This dynamism has made the value-added chain from an invention towards the approval in the market longer and more complex, which is best demonstrated by the entrance of two new organizational species to which I will turn next: Contract Research Organizations (CROs) and virtual drug companies.

4.5.4 Contract Research Organizations and Virtual Drug Companies

Although CROs and virtual drug companies do not necessarily apply biotechnology in the strict sense of the definition used in Chaper 1, their inclusion in this survey helps understanding ongoing organizational changes of the pharmaceutical industry. Like biotechnology firms involved in drug discovery, they fulfill relevant tasks that large pharmaceutical corporations used to conduct in-house in the past. CROs carry out very little R&D on their own. Instead, they are a service provider that coordinates and carries out clinical trials for pharmaceutical and biotechnology firms. Starting out in the beginning of the 1980s as small, specialized boutique firms, such companies have grown substantially with regards to size and number, as well as the services offered. By the early 2000s, the global CRO industry was estimated to have a market size of $8 billion (Mirowski and Van Horn 2005). Included in this survey (MA 33) is one of the oldest companies of its kind, founded in 1983, which currently belongs to the top ten global CROs. A transnational corporation with headquarters in Boston, the company had $565 million in annual revenues and carried out testing for all major pharmaceutical firms. According to the CRO representative interviewed, particularly biotechnology firms were requesting their services as they could not rely on structures built in-house to conduct and manage clinical trials. Conversely, CROs are known for a high turnover in staff and biotechnology executives repeatedly highlighted that they are an attractive source to hire from. CROs have certain ‘sweat shop’ characteristics, because their staff is relatively low paid and less trained than counterparts in large pharmaceutical firms, while being at the same time well specialized in handling a high throughput of trials and data management (ibid., p. 519).

Also virtual drug companies do not carry out their own R&D. Instead, they coordinate the steps necessary to move a technology or a drug candidate, normally protected by IPRs, closer to the market. Included in this survey were four virtual drug companies whose common business rationale was the value that their coordination efforts added along the drug development chain. In order to get remunerated for this effort, companies pursued different strategies as to when and how they got engaged with a major pharmaceutical player. For instance, one company (MA 17) sought opportunities in the market for drugs below Big Pharma's blockbuster drug threshold of one billion dollars a year in sales. As an intermediary in the drug development pipeline it licensed early-stage technologies, coordinated clinical trials, and ultimately hoped to sell or license them back to a big pharmaceutical company. Two other virtual drug companies licensed drug compounds that had been abandoned or had lost patent protection. These compounds were then retooled into treatments against a different disease and run through clinical trials for regulatory approval for these new indications. Once approved for the US market, they were licensed for production and marketing to a pharmaceutical company. One manager derided this approach of working with the leftovers of the blockbuster drug development routine as '*Pharma Junk*' (Interview SF 7), but the more correct description would be 'Pharma Recycling.'

A virtual mode of operation also implies less overhead for staff and laboratory space, which allows companies to react quickly to the ups and downs of the destiny of their drug developments. One company surveyed sold the US marketing rights for a product for $20 million to a German multinational. As they had no successive financing in sight, they

decided to lay off the majority of their 110 employees and revamped their business model towards a virtual drug company with freelance staff. At the end of the day:

> *"It's all about the drug. In the future, a big pharma company might license our developed drug or take over the entire company - whatever is more advantageous for big pharma to get the drug."* (Interview SD 22)

In sum, virtual drug companies prove to be an efficient vehicle to exploit niches in the current drug development regime. Ultimately, their coordination effort is remunerated because they re-integrate activities that have been fallen by the wayside, back into the blockbuster drug development regime.

So far, this analysis of the biotechnology industry followed VoC's approach as to where LMEs such as the United States should provide a comparative institutional advantage for a rapidly innovating industry, such as biotechnology. Yet parts of this institutional support structure – in particular the protection of intellectual property – are at the same time key to market-driven innovations, but also slowing down the process of rapid innovation. Moreover, I argue that creative destruction and rapid innovation for the time being did not change the power relations in the drug development process. Both arguments were confirmed in particular by the genomics industry. Genomics companies highlighted how creative destruction worked in one of the most advanced and financially risky fields of the biotechnology industry, but also the extent to which the industry's center of gravity is dominated by the logic of pharmaceutical research and development.

This section has illustrated some limitations of the categories suggested by the VoC-approach to explain the coordination activities in the biotechnology industry. Most of these shortcomings were due to the specific nature of innovation with which this industry deals with. Moreover, VoC by definition cannot account for sub-national differences, for instance of certain support structures. The geographical proximity of certain institutionalized support structures such as scientific institutions, human resources, and funding all are important reasons for sub-national clustering of the biotechnology industry, which will be addressed next.

4.6 Biotechnology's Embeddedness in Regional Clusters

4.6.1 Proximity to Science

This section will investigate the reasons for why the biotechnology industry tends to cluster around crucial support structures, such as research institutions, human resources, and capital. I will start my investigation of the particular logic of clusters with the relevance of proximity to universities. This relationship deserves special scrutiny, as traditionally the interrelatedness with scientific research and academia has been considered to be one of biotechnology industry's signature features (Kenney 1986; Zucker, Darby, and Brewer 1998). This survey found that more than one third of all companies included were the result of a formal spin-off. A spin-off was defined to include only those cases where the new founders took with them the right to use proprietary technologies.

Table 4.12: Share of Spinoffs among all Companies Established*

	NY	MA	MD	SF	SD	AVGE
Total	23.3	36.4	28.0	48.0	50.0	37.1
Universities	20.0	21.2	8.0	36.0	6.7	18.4
Federal Research Institutes	3.3	3.0	12.0	0.0	0.0	3.7
Other Research Institutes	0.0	6.1	0.0	0.0	20.0	5.2
Company	0.0	6.1	8.0	12.0	23.3	9.9

*(includes only companies where founders left together with proprietary technologies)

Universities were the major source for establishing such new companies, accounting for more than half of all spin-offs (Table 4.13).

Table 4.13: Source of Spinoffs

Among Spinoffs (%)	(n=7) NY	(n=12) MA	(n=7) MD	(n=12) SF	(n=15) SD	(n=53) AVGE
Universities	85.7	58.3	28.6	75.0	13.3	52.2
Federal Research institutes	14.3	8.3	42.9	0.0	0.0	13.1
Other Research Institutes	0.0	16.7	0.0	0.0	40.0	11.3
Company	0.0	16.7	28.6	25.0	46.7	23.4

In this sense, nothing seems to have changed with regards to the central role of academia for the provision of biotechnological science. Moreover, these findings also corroborate with one crucial prediction of the VoC-approach: Technology transfer in LMEs is predominantly fostered by the movement of highly trained staff. It comes as no surprise therefore that, when asked why a company was at its current location, proximity to scientific knowledge was mentioned prominently in all five regions. Below this general agreement, however, there was a more subtle picture. It had to do with the varied roles that scientific research institutions played as support structures for biotechnology firms, particularly with regards to ongoing collaborations and human resources.

For instance, it became apparent that there was a hierarchy among universities concerning the leverage these had when collaborating with for-profit corporations. One aspect of this were the different policies vis-à-vis their faculty setting up biotechnology start-up companies that universities put in place. Some institutions gave their academics the chance to carry out research in their university laboratories that benefit their private companies. For example, the University of Medicine and Dentistry, New Jersey (UMDNJ) benefited one interviewed company (MD 7), whose Chief Scientific Officer could use the laboratory that belonged to him as a faculty member for research that dovetailed with the interests of his company. This research had already rendered six patents, which the professor filed through the university. While the fees were paid by his company, the professor's firm gained the right to exclusively license back these technologies from the university.

In a similar vein, another company was founded around a technology licensed from and invented at Harvard University (MA 23). Yet the inventor decided to leave Harvard for Boston University, because he wanted to remain engaged in this new start-up company. As a faculty member of Boston University, he could carry out drug discovery research funded by his company, which would also have the first right of using the results. Harvard's policies prevent such relationships. By statute, inventions of Harvard faculty are the property of the university and companies in which faculty has a stake do not enjoy preferred treatment regarding licensing of a technology.

Research universities such as Harvard and the Massachusetts Institute of Technologies (MIT) therefore established Technology Licensing Offices[41] that help them commercializing their inventions. The benefits from this can be substantial: One survey of the economic impact of MIT spin-offs estimated that MIT graduates and faculty were involved in the formation of 4,000 companies, which employed 1.1 million people, had annual world sales of $232 billion, and if formed an independent nation, based on these revenues would make it the 24th largest economy in the world (Bank Boston 1997). As for Harvard University, in 2008 alone, Harvard's technology licenses generated more than $21 million in revenues[42].

In addition to generating revenues, technology transfer offices also have to negotiate the respective realms of interest with the faculty. To prevent MIT professors from exploiting university students and laboratory facilities for the benefit of their own companies, MIT has put in place a policy to separate the interests of the university from that of its faculty. Corporations in which MIT staff has a financial stake cannot sponsor research at MIT. Moreover, faculty is only allowed to dedicate one day a week to work outside the university, such as for consulting or for founding a company. However, as the representatives of the MIT Technology Licensing Office admitted, a number of IT companies were started around these guidelines.

[41] The following section profited from interviews with representatives from Harvard's and MIT's technology licensing offices in January 2002.
[42] See the website of the Harvard Office of Technology Development: http://www.techtransfer.harvard.edu/mediacenter/annuals/stats/index.php#revenues (retrieved March 23, 2009)

While they are particularly hard to enforce with regards to software development, apparently they were also applied with some grain of salt elsewhere as the case of Professor Erik Lander at MIT's Whitehead Institute for Biomedical Research demonstrates. Lander was not only prominently engaged in the Human Genome Project, but he also who co-founded Millennium Pharmaceuticals, a company that continued to fund research at the Whitehead Institute.

Self-confidence about the economic value of their scientific expertise was not limited to these elite private research universities in Massachusetts. In both San Diego and San Francisco, biotechnology executives complained about the impossibility to collaborate with the public institutions of the University of California (UC) system. One company founder from San Diego for instance, contended that

> "*the patent system of UCSD* [University of California San Diego, VL] *makes it hard for our company to use technologies from the university."* (Interview SD 26)

Apparently therefore, the universities of the UC system, which were so instrumental in establishing the scientific basis of the biotechnology industry[43] are today shunned as collaborators because they have become too capable as for-profit-managers of their own intellectual property. Obviously, the coordination of research interests by means of individual commodification and contractualization, which is so crucial to the setup of the United States' successful biotechnology innovation regime, also has its drawbacks. It is

[43] See for instance Zucker and Darby (1996).

therefore a matter of interpretation and political negotiation among different actors, a topic that will be revisited in chapter 7 (see 7.4).

4.6.2 Clustering of Trained Staff

At the same time where top-tier research universities were not always cherished as research collaborators, they were considered an important source for knowledge as faculty could be brought in as consultants. For similar reasons, corporate managers considered two high-profile biomedical research institutions – The Scripps Research and the Salk Institute – as an advantage for San Diego. Whereas the Scripps Institute allowed collaborations in which outsiders could command the IPR, as was the case for Novartis (see 2.7), Salk Institute policies prevented this[44]. But faculty and scientists from both research institution could be hired as consultants, adding to the relevance that proximity to trained human resources has for biotechnology companies. In the words of a company representative in San Diego:

> *"We are here because of the critical mass of other biotech companies and R&D institutions… not so much for collaborations but for recruitment of trained staff - trained staff in general."* (Interview SD 4)

This is reflected by the recruitment pattern, not only in San Diego, but throughout all regions included in this survey. Almost four fifths were hired from within the region, which indicates the tendency of clustering of biotechnology companies and scientific institutions. It is also noteworthy that more than one fifth of the people working in the biotechnology

[44] (Interview Salk Institute technology transfer office, January 23, 2003).

industry were born outside the U.S., which indicates the attraction that this industry has for people with migration background that are particularly highly educated.

Table 4.14 Geographical Distribution of Recruitment

Recruitment	NY	MA	MD	SF	SD	AVGE
Within Company	0.3	7	4.3	0.4	0.4	2.5
Regional	83.3	65.2	85.6	89.4	69.4	78.6
National	14.5	23.6	8.5	9.4	28	16.8
International	3.8	4.2	1.6	0.8	2.2	2.5
Not US-born	19.0	20.6	18.1	28.6	28.2	22.9

The generally high level of payment in the biotechnology industry mentioned earlier cannot explain the competitive advantage of certain regions over others. Contemporary studies on competitiveness and its protagonists, the 'creative class' (Florida 2004, 2005), therefore highlight the importance of cultural factors. According to this logic, knowledge-based industries, including biotechnology, tend to prefer certain regions and find it easier to attract the most capable human resources. Consequently, a vibrant biotechnology cluster would depend not only on the quality of its life sciences, but also on its quality of life. This was confirmed in different ways by different interviewees. For instance one company executive (MA 8) explained how soft factors are indeed important for Boston. Whereas cities like Chicago or New York are dominated by other activities, such as production or finance, in Boston the environment was more appreciative of biotechnology: *"It's a sexy dinner party topic."*

Somewhat less glamorous, from the perspective of an employee working in a volatile, high-risk industry, clusters were also considered a safety net beyond the company by whom

one is employed. The majority of biotechnology employees had been laid off at least once, but a cluster provides some stability, because it allows people to stay in the region:

> *"Working in biotechnology means working in a high-risk business. It is not unlikely that the company I am working for now may go out of business at one point…If there are other companies around and I get laid off, I can find a job easier without having to move, without having to sell my house, and without having to find a new school for my children."* (Interview (MA 22)

In absence of any formalized, legal, and collective mechanisms to safeguard employees' wellbeing, the loyalty of employees in this industry, therefore, never is, never can be unanimously focused on one single company. Clustering is one consequence of this market-led mode of rapid innovation, unaccounted for by the VoC typology, which does not see geography as an issue.

Yet 'geographic stickiness' determines companies' destinies also in another way: Often it is the location of the founders that determines where a company will reside. In both San Diego and San Francisco, the question why a company was at its current location, the most frequently mentioned reason (50 and 52 percent, respectively) was that the founders had already been there and wanted to stay. The interviews therefore did not conform to postulations about knowledge-based industries being more footloose than production-based ones (Hilpert 2003). Moreover, the findings highlight the limits of the assumptions in VoC that coordination in LMEs is dominated by contractual agreements. Even such

economically strategizing actors as those in the biotechnology industry are to a large extent motivated by non-formal motives too that show the embeddedness of economic activities within social ones. This will become even more obvious in the next section, which looks at the discrepancy between formal and non-formal agreements between investors and recipient firms in the biotechnology industry.

4.6.3 Proximity to Capital

Venture capital was the single most important source of money for the majority of companies interviewed (see Table 4.6 above). Yet there were surprising differences among the regions that deserve to be explored further. For example, one would assume that in New York, the world's leading financial hub, the proximity to investors should also benefit the biotechnology industry. This was the case for one biomedical device company, which was set up by Wall Street bankers who invested part of their own money to expedite the establishment of their own, new corporation. To expedite the establishment of their own, new company, according to one of the founders,

> "*writing a cheque is faster and easier than applying for funds.*" (Interview NY 16)

In the end, they did both and used their financial expertise to raise $30 million from different VC funds. However, this was the only company surveyed in New York where there was an obvious link to the investment community and that was profiting from local VC. While there is obviously no scarcity of funds, they are not necessarily spent locally. This was indicated by one other company representative who complained that

"Private money tends to overlook the no-boom regions such as Long Island and would rather pour its resources into established clusters such as Boston/Cambridge." (Interview NY 7).

In fact, looking at data available for overall VC investment in biotechnology companies, the New York/New Jersey conurbation is only in the third position after California and Massachusetts (Table 4.15):

Table 4.15: States Ranked by VC Investment in Biosciences, 2002-2007

Rank	State	Total in $ Million
1	California	20,743
2	Massachusetts	7,091
3	New Jersey	2,778
4	Pennsylvania	2,772
5	Maryland	1,957
6	New York	1,225

Source: Battelle 2008, p. 38

The statistics above indicate the dominance of VC investment that was also confirmed during the survey. The strength of the Californian VC industry and access to funding was repeatedly mentioned as the main reason for locating a company in California. Specifically, 48 percent of all companies surveyed in the San Francisco Bay Area were enjoying funding from a local VC firm (see Table 4.6 above) One VC firm representative in San Francisco explained:

> *"VC does not like to travel. I can find enough potential for high returns on my investment in this region."* (Interview 9/09/2003)

The fact that VC money is so hesitant to travel harks back to the mode of operation of VC firms mentioned earlier: Typically, a VC firm not only provides financial support, but also advice and managerial guidance, roles that becomes easier when the biotechnology company is nearby. Similarly, a study by Powell et al. (2002) on the spatial clustering of biotechnology and VC found that local support is normally geared at younger companies, whereas external investments tend to go to firms that already have something more to 'show', e.g. a late-stage clinical trial or even a marketable product. Conversely, as VC firms become larger and more experienced, they invest more in both younger and further away companies, a trend that appears to be somewhat modulated by the VC's regional origin: Whereas Boston VC money tends to stay regional, New York money roams the country and Bay Area VCs start out in California before looking for opportunities elsewhere.

In this regard, the survey demonstrated that VC located in the Bay Area was still close enough and readily available to be invested in San Diego. There, almost two thirds of companies received venture funding, albeit less from local investors. Local funding in San Diego came less often from VC, but from 'angel investors'. Angels are wealthy individuals who invest in a company at an early stage of its development. Usually angels invest less than $1 million per startup. Some companies found that although venture funding could

provide the larger amounts of money, VC firms were only very slowly – if at all – evaluating their projects and therefore, it was better relying on angels and private investors:

> *"If you know the people with the checkbooks, you don't have to beg for VC and wait until they approve your business plan."* (Interview SD 8)

The proximity between scientists and angel investors adds to the advantages of clusters. In the words of one other biotechnology executive from California:

> *"There are a lot of angels in San Diego, who usually invest in people they know…Face-to-face contact is critical. Investors invest in people, not products."* (Interview SF 11)

San Diego is interesting in this regard, because some companies explicitly mentioned how they benefited from local entrepreneurs and angel investors who had made their money in information technologies and military-related technologies. The close relationship with angel investors was often mentioned a reason for why the company was at its current location. San Diego companies profited from informal networks such as the south Californian angel investor network 'Tech Coast Angels'[45], whose members invest only in southern California companies. Similar to the screening criteria of a VC investor, this angel network only invests in firms that fulfill certain criteria, such as an annual revenue potential of at least $50 million; overcome barriers to market entry such as patents; and have an exit strategy with regards to who will eventually acquire the company. In sum,

[45] Tech Coast Angels claim to be the world's largest organization of its kind (see www.techcoastangels.com).

compared with VC angel investors further intensify the already personalized relationship between money and science.

On a theoretical level, VC and angel investors demonstrate the embeddedness of economic activities in social activities also for the biotechnology industry: Rational actors make their business decisions not only based on market considerations. While all of the different steps of their business engagement may be based on contracts and may be executed in a 'formalized' manner, they ultimately are existent only because of trust. Even more, whereas the VoC approach has little room for such tacit, non-contract-related, knowledge for rapid innovation in LMEs, I argue that the comparative advantage of certain regions in the United States is based on just that: A comparative institutional advantage for biotechnology locations ensues when in close proximity investors and recipients of funds share a common, non-formalizable understanding of their innovative activities: In short, trust among the protagonists makes the setup more dynamic and more innovative.

4.6.4 Proximity to Other Companies

So far this inquiry highlighted the benefits of biotechnology companies embedded in clusters due to the proximity between scientific institutions and financial investors. But clustering is first and foremost related to companies. So putting aside the previously mentioned 'safety net' function for people who may be laid off, how much of a blessing is it to have other biotechnology companies in close proximity, and for what? One answer to this is, again, human resources, the demand for which very much depends on the developmental stage of a company. For instance, a research-dominated biotechnology

company may need different skill sets as soon as it is getting closer to having its first products approved by the FDA. These transitions are sometimes helped by the rate of attrition of companies, but also by general trends in the pharmaceutical industry:

> *"The mergers of Big Pharma companies in the late 1990s released staff that was then hired by biotech companies wanting to become drug companies."* (Interview MD 3)

But not only mergers, also company takeovers release large numbers of staff, taking with them their scientific and managerial expertise. For instance a number of San Diego companies included in this study were started by individuals who left a first-generation biotechnology company, Hybritech, after it was acquired by the multinational drug company Ely Lilly in 1986. Interview partners described how the clash of culture between an innovative biotechnology firm and a large, bureaucratized transnational drug firm, led to an exodus of trained staff from the acquired biotechnology firm.

This is an important aspect of how creative destruction works in practice. It is also a mechanism for technology transfer, and it is in line with what VoC predicts for liberal market economies. Yet not always do successful companies have to be destroyed first to give rise to the creation of new firms. On the contrary, it seemed that a sign for a matured cluster is the existence of thriving companies that function as an institutional frame and a nurturing ground to spin off new start-up companies. This was for instance a side effect of the successful genomics company in Massachusetts mentioned earlier (see 4.5.1). That company acted as 'seed incubator' as many employees left for other biotechnology startups

or set up their own firms. This is not only different from publicly funded incubator programs, but also from the beginning of the industry in the 1970s when this function was fulfilled by universities. Referring to the critical role of large-scale biotechnology companies for nurturing the right talent, and justifying why his company was in San Francisco, one corporate executive made the following calculation:

> "*Genentech* [the world's second largest biotechnology company, VL] *has 5000 employees and a turnover rate of 10 percent. In other words, 500 employees leave Genentech every year – this is a highly attractive pool to hire from."* (Interview SF 17)

One would assume that the clustering of companies would also facilitate their collaborations. Yet when asking firms about their collaborations, which included only those sealed by a contractual agreement, the opposite turned out to be true (Table 4.16). Surveyed companies had only 17 percent of their collaborations with local partners. More than two thirds of the formalized collaborations were on the national and international level (respectively 44 and 25 percent).

Table 4.16: Geography of Collaborations

Collaborations (%)	**NY** (n=29)*****	**MA** (n=32)*****	**MD** (n=24)*	**SF** (n=24)*	**SD** (n=30)*	**AVRG** (n=139)*
Local	23.6	11.0	7.8	13.0	27.5	16.6
Regional	18.1	12.0	25.3	7.7	7.2	14.1
National	39.3	50.0	43.8	49.7	37.1	44.0
International	19.0	27.0	23.0	29.6	28.2	25.4

***** Formalized by contract. Excluded are companies with >50 unspecified collaborations

These findings seem to indicate that proximity to other companies mattered most with regards to tacit transactions and technology transfer due to mobile, highly trained

individuals, but not so much for cooperation to conduct joint business. It is therefore particularly interesting to look at the attraction of clusters for foreign companies and their reasons to establish a local subsidiary.

Nine of the companies included in the survey were the subsidiary of a foreign company. One of the purposes repeatedly coming up throughout the interviews was that Non-American corporations were attracted to enter the United States' huge and profitable market. Yet for this reason alone, a subsidiary may as well have been opened in Iowa, North Dakota, or Kansas. Instead, foreign companies that choose to locate their subsidiaries in the regions surveyed did so, because of a combination of advantages that these clusters of biotechnology innovation could conceivably offer. For instance, one Massachusetts-based diagnostics biotechnology company (MA 32) was acquired by a German multinational pharmaceutical company. The buyer was attracted and willing to pay $11 million, in part, to acquire the company's IPR portfolio of 50 patents worldwide, but also to have a *pied-à-terre* in the research community in Massachusetts. While the diagnostics company had some revenues from selling diagnostics kits, it did not break even. Nevertheless, the pharmaceutical mother company kept the loss-making subsidiary afloat as its diagnostics R&D hub in North America.

Having an American R&D department at almost any cost was also the reason why one other large German pharmaceutical firm bought a cancer drug development biotechnology company surveyed in Massachusetts. This firm was acquired for $70 million, without having a single marketable product and continuously loosing about $15 million per year.

While eventually the German pharmaceutical firm should profit from marketed products, for the time being:

> "*They are a kind of a sugar daddy. They do whatever it takes to have access to our research expertise.*" (Interview MA 1)

This division of labor was even more elaborated for another firm in San Diego, which was bought by a multi-billion-dollar-worth Japanese pharmaceutical company. Historically, Japanese drug firms were focused on their huge, protected, domestic market (see 2.7). In this particular case, the Japanese firm wanted to launch a product on the American market for the first time, and towards that end, bought up a company in San Diego to tap into the pool of scientific expertise available there. According to the interviewee

> "*we are loosing 28 million dollars a year, but we have a lot of autonomy, because the marketing strategy* [of the Japanese mother company, VL] *is not clear at the moment.*"

It seems that this one-level-removed, at-arms-length conduct of business added to the generally derogatory view that research-oriented biotechnology firms had of large pharmaceutical companies. It is ultimately – again – a cultural conflict about profitability of research endeavors between two different types of business. Having a foreign paymaster seemed to obfuscate the power relations from the perspective of biotechnology firms in the United States.

Conversely, the hopes of foreign companies to profit from regional scientific excellence did not always pay out. For instance, one Japanese medical device company interviewed set up a subsidiary in the San Francisco area to carry out software development and R&D and profit from that location's strength in these fields. However, at the time of the interview, strategies had changed and all technologies were developed in Japan. The location was still considered to be an advantage as it is close to their biggest customer as well as many other companies in San Francisco and San Diego. Equally mixed were the experiences of a German drug development company, which entered a joint venture with the world's largest biotechnology firm Amgen (CA). As a prerequisite for receiving $40 million from Amgen, the joint venture had to be in the Bay Area. When Amgen left the joint venture in 1997, the San Francisco subsidiary was downsized to function only as a business hub to acquire companies in California and in the Boston area. Equally important as to tap into the pool of knowledge was the proximity to venture capital and the US stockmarket, because, according to the interviewee, *"Public money is harder to raise in Germany"*. (Interview SF 7)

These statements illustrate some of the incentives as well as the high hurdle for entering the American market. Obviously, foreign entrants need to be prepared for continued financial subsidies. The most likely candidates are therefore large companies from other advanced industrialized nations, which prefer to set up subsidiaries in biotechnology innovation clusters. The examples of unsuccessful entries demonstrate that many times the expectations have been too high. Yet their hope is that by being embedded in one of the leading biotechnology clusters, the overall business will ultimately profit from the

combination of market access, research capacities, and capital. In other words, by shifting certain activities into these specific clusters of biotechnology innovation, foreign companies want to profit from the institutional arbitrage that the support structures of the political economy of the United States provide for (Hall and Soskice 2001, p. 57).

While these last contentions revolved around the shortcomings of the VoC approach with regards to underestimating the importance of non-formalized means and ways of coordination among business actors, there are also other spheres of the political economy (for instance in science funding and regulation), where biotechnology takes much more advantage of formalized, state-created coordination structures, than VoC would ascribe to the U.S. as a liberal market economy. These will be addressed next.

4.7 Public Funding for the Biotechnology Industry

Whereas the majority of respondents considered public financial support – either federal or from the states – only the second-best solution for their business, this verdict depended much on where companies or clusters were in their development cycle. Most federal support programs mentioned by interviewees fell into the Small Business Innovation Research (SBIR) program and its sister entity, the Small Business Technology Transfer (STTR) program. The purpose of the existence for these funding mechanisms is the development of new ideas and the proof of concept. SBIR and STTR awards are either grants or contracts and have a volume between $100,000 and $750,000. There was a

general approval of how these federal grant schemes worked. Of the surveyed companies, 56 percent had used such a grant and 35 percent found it useful. (Table 4.17):

Table 4.17 Federal and State Support Programs

Support programs		**NY**	**MA**	**MD**	**SF**	**SD**	**AVGE**
Federal:	awareness	87.7	69.7	92.0	72.0	90.0	82.3
	usage	63.3	45.5	76.0	40.0	53.3	55.6
	relevance	46.7	24.2	48.0	24.0	33.3	35.2
		NY	**MA**	**MD**	**SF**	**SD**	**AVGE**
State:	awareness	70.0	9.1	88.0	36.0	50.0	50.6
	usage	40.0	0.0	68.0	28.0	20.0	31.2
	relevance	30.0	0.0	64.0	12.0	6.7	22.5
	local	36.7	0.0	28.0	8.0	23.3	19.2

For a number of smaller companies interviewed, these federal financial support mechanisms often played a decisive role in moving ahead. The flipside of that same coin was that larger and more advanced companies often found the grant application procedure too cumbersome for too little money. For them, an SBIR grant barely covers one month of the costs of a clinical trial. Moreover, applying for funding was complicated by considerations regarding intellectual property rights. While some company representatives contended that receiving public money made it more difficult claiming intellectual property afterwards, others criticized the peer review process upon which SBIR grants were distributed, because it would provide insight into the technologies to competitors who may use such information for their own advantage. Despite such criticism, these federal programs proved to be an important support structure for a segment of the biotechnology industry that adds to the comparative advantage that the United States can muster.

The overall assessment of state programs was decidedly less favorable. Although every state by now prides itself of having a biotechnology support policy framework (Battelle 2008)[46], corporations included in this survey generally gauged them less relevant to their work than federal support programs. Less than a third (31 percent) had used them and less than a quarter (23 percent) found them useful. There were, however, important geographical differences. In the Boston region, for example, there was little awareness of state programs and not a single company had ever used one. Interviewees explained that services that in theory could be delivered by a state or public program, such as providing incubator space or helping with finding investors, in practice in Massachusetts are provided by private entities. One other example was the outsourcing of $50 million of a state technology fund, which was managed by a VC firm. Overall, the fact that Massachusetts programs were irrelevant to companies may also be an indication for the maturity and sophistication of the biotechnology industry in the Boston area.

Also Californian support programs were considered useful only by a minority of firms, respectively 12 percent in San Francisco and 7 percent in San Diego. Yet in San Diego, 23 percent of interviewed companies profited from local support. Some of it was generated completely without public monies, such as informal networks of private 'Angel' investors (see 4.6.3 above). Another local support institution was the public-private partnership program by the UCSD, which brings together research institutions, investors, corporations, and professional services providers to accelerate the commercialization of innovations.

[46] An overview is available online at http://bio.org/local/battelle2008/

Of all regions surveyed, Maryland's state support programs scored highest. State initiatives were considered relevant by 64 percent of interviewed companies, and were used for a variety of purposes. For instance, one firm (MD 4) praised the research partnerships that it could enter with the state-funded University of Maryland. While the corporation made a small payment to the university, the state matched those funds, but the company retained the rights to the research results. In effect, the state of Maryland paid twice so that the university could provide contract research services to a private company. Maryland was also lauded for providing state grants that could be used very aggressively for international trade and business to enter new markets. One other firm (MD 8) was granted $20 million by the state to set up a contract manufacturing facility in the region. While the state retained the ownership of the facility, the company leases back the facility from Maryland and the pursuits went into the budget of the statewide biotechnology interest group organization, MDBio. Last but not least, the state was also funding eleven incubators for start-up companies. The high approval rate of the Maryland biotechnology state initiative is all the more noteworthy as the companies interviewed were also the ones that took most advantage and judged useful (76 and 48 percent, respectively) of available federal support. To some part, this may be explained by the geographical proximity of the federal institutions in Maryland, and especially the NIH. But to some part, the dependence on public support may also express that the Maryland biotechnology cluster is less developed, diverse, and strong than other regions. Maryland's biotechnology industry demonstrates also that in the United States as a representative of liberal market economies, the neoliberal paradigm of public non-interference in business activities is never a principled demand. Rather, if it is in the interest of strengthening business interests, the interference of the

public hand is willingly taken into account. This is the complex role that the neoliberal state plays as it becomes a national-competition-state (Hirsch 1995). Interviews also illustrated two other functions of the states in this regard crucial for their business endeavors: The structure of the American healthcare market, as well as the regulatory environment for pharmaceuticals. Both will be addressed next.

4.8 Healthcare Markets and Regulatory Hurdles

VoC, like other theoretical approaches, seeks for comparative institutional advantage in those coordination structures provided for by the institutions of the economic supply-side. This neoliberal view on the supply-side leaves out the crucial role that coordination of the demand-side plays for economic actors. Throughout the interviews with biotechnology entrepreneurs, the demand side was regularly brought in when interviewees were asked about the relevance of the United States healthcare market. Emblematic for many others was the following view of one executive:

> *"The American Healthcare market is the least regulated and the most profitable… Higher prices for our products mean that we can get back our investment on R&D faster."* (Interview MD 5)

Yet there were also others, who alluded to both the United States and Europe as the two most profitable markets:

> *"Presently, our most important goal is to get two products* [one of which is already marketed in Europe, VL] *on the US market. For the future of our business, FDA and EU approval are key"*. (Interview MA 16)

This position pointed to the pivotal role of the FDA. Except for those companies that were engaged in agricultural and environmental biotechnologies, the FDA was the ultimate regulatory agency for the firms surveyed. As it turned out, the FDA was considered one of the support structures of the political economy of the United States. In looking for institutional arbitrage, notably between the United States and Europe, biotechnology actors considered the FDA playing a positive role for the United States. Timing is of the essence and often companies that conducted several clinical trials in parallel, did so also outside the United States. Ultimately, however the purpose was to get approval in United States, *"because it is the faster process."* Equally important, companies wanted to obtain regulatory approval for their products in United States first, because *"That is where the money is"* (Interview MD 5). Not all interviewees agreed, however. As one side effect of the regulatory environment in the United States for drug approval and marketing it was contended that

> *"the FDA has censoring power over marketing…Price controls* [in Europe, VL] *should be loosened up, because the United States' high payback on R&D subsidizes EU's lower prices."* (Interview SF 2)

Again, we see how the role of the neoliberal state has changed: instead of being a hurdle for entrepreneurial activity, its interventions become an asset in the international competitive arena. The question of extending FDA's authority with regards to pricing – both domestically and internationally – will be revisited in the next chapter. It is an important systemic issue for how the American variety of capitalism (under neoliberal premise) offers comparative advantage for biotechnology actors.

Yet the role of the FDA is also crucial for understanding the changes within the value-added chain of drug development. In the past, large pharmaceutical firms used to have several in-house candidates in the pipeline towards drug approval, and one failure would not sink the entire company. Today, however, when pharmaceutical firms are outsourcing the research towards several smaller corporations, they are also outsourcing the risk. Biotechnology or any other corporations that depend on the approval of a single product, will most likely be wiped out if that approval is denied. During many interviews therefore, the FDA's verdict on the outcome of clinical trials and ultimately, market approval was the great divider between the making and breaking of a company. In the words of one of executive whose company had just enough money to finish a clinical trial:

> *"After a successful market approval, we may be acquired. But if we fail again, this will be the end for us."* (Interview SF13)

FDA's approval decides on which side of capitalism's perennial gale of creative destruction a company will ultimately come down. Hence, expediting the market approval

procedure, as well as knowing intimately the approval process, is an asset that specialized business can capitalize on. This was manifested by two companies, not coincidentally located close to the FDA in Maryland, which used their insider knowledge of FDA approval procedures and its proximity to the regulatory agency to help companies get their drugs approved:

> *"A blockbuster drug is worth $ 1 billion in sales annually. You do the math. One month delay is worth almost $100 million. To know where the approval procedure may get stuck can save a lot of time and money."* (Interview MD 20)

These firms capitalize from the personal contacts established over the years. Again, as was the case with the intimate relationship between investors and recipients of funding (see 4.6.3 above), such specialized coordinating businesses are hardly possibly only on 'formal' or 'contractual' terms. They highlight the tacit, informal component of America's comparatively advantageous biotechnology innovation model that cannot be subsumed under the categories for liberal market economies of the VoC approach.

4.9 Concluding Remarks: Pipelines, Pipers, Paymasters

This chapter took off from a relational view on the firm and business actors who pursue their individual interests under the circumstances of a given set of institutions. Findings were in line with some of the predictions made by the VoC framework for how the United States as a liberal market economy would provide a comparative institutional advantage for

a rapidly innovating, advanced industry, such as biotechnology on institutions of the political economy such as the financial systems and the models of corporate governance; industrial relations and education and training; and inter-company relations.

On the other hand, the framework did not completely explain a number of issues that were equally important to the innovation model in biotechnology. To begin with, it is not clear how rapidly innovative biotechnology indeed is. Whereas technological turnaround and creative destruction may be fast, drug development is not. The genomics industry proved to be a case in point as this sub-industry, despite its rapid technological progress did not change the approach towards new drugs after all. Second, not all relationships that matter for the biotechnology industry are of a formalized, contractual nature. The 'tacit' aspect of knowledge that leads to the close proximity between biotechnology and scientific institutions is equally relevant for the intimate relationship with high-risk venture funding. Lastly, interviews highlighted the crucial role of state interventions on various levels: Start-up firms that profit from direct government subsidies, the importance of patent enforcements, the gatekeeper function of the FDA to the world's most profitable healthcare market.

The way in which biotechnology actors rationalize their behavior and make strategic business decisions therefore highlight the different parts of the institutional support system that surrounds them. Looking at these corporate actors allows drawing some preliminary conclusions about the U.S. biotechnology innovation regime. Biotechnology remains creative destruction at work, a dynamic industry with a high turnover of companies, capital,

and people. The hegemonic business logic is dictated by its most advanced players, those companies that are engaged in the development of new pharmaceutical drugs. By comparison, other business models and fields of application such as agriculture ultimately have to measure up with the profit expectations that the world of pharmaceuticals has created.

Many companies mentioned the profitability of the American healthcare market as their primary reason for first launching their products in the United States, an attraction that also encouraged foreign companies to set up a subsidiary there. Another reason why many foreign companies want to be located in the United States is the access to the most advanced scientific knowledge and the regions surveyed had in common that they hosted a number of the world's most advanced scientific research. But academic institutions have become increasingly aware of their bargaining position, particularly regarding the intellectual property they accumulate, which makes it at times difficult for private companies to collaborate with them. Interviews documented that not only for academia, patents have become both a bargaining chip and a roadblock. In both capacities, intellectual property claims have become instrumental to the functioning of the current biotechnological innovation regime.

For the technology supply side of this regime, federal support programs were considered to fulfill a useful role circumscribed to the early stages of a company. State programs had a similar effect – if any - only for Maryland, the least mature of the surveyed biotechnology cluster. Instead of receiving public monies, most companies considered venture capital as

more important for their growth. In fact, VC was the booster for creative destruction in the biotechnology industry as investors' speculations on future value was more important than current profits. Nowhere has this become more obvious than with the genomics industry. But after a brief rise towards stellar market valuations, this avant-garde within the value-added chain of drug development came to a crashing halt as the technological hopes could not render real products and profits. At the end of the day, these imperatives continued to be dictated by large pharmaceutical corporations' blockbuster logic according to which a drug worth pursuing has to be worth a billion dollars of sales a year.

So if VC was the booster, the cash of pharmaceutical companies was the fuel for the long-term journey of biotech companies. For most firms, this journey was to become an outsourced research laboratory – bearing the brunt of the risk if a product was not approved by the FDA – but with the hope for huge remunerations if successful. Outsourcing R&D risks to new biotechnology firms and the rise of biotechnology as a research sub-unit coincided with other organizational innovations. Together with new organizational entities, such as virtual drug companies and contract research organizations, biotechnology firms became part of a taylorist set-up for pharmaceutical R&D. This more networked alternative replaced the old fordist, hierarchical organization of previous pharmaceutical R&D endeavors, while not challenging the market power relations. So far, the biotechnology revolution did not take place.

While biotechnology as an industry therefore became solidly embedded in the market dynamics and the drug discovery logic of big pharmaceutical companies, it became also

embedded in geographically circumscribed clusters. Clusters provide proximity to scientific knowledge, capital, and other companies. This combination makes clusters particularly attractive for foreign companies that want to profit from institutional arbitrage for biotechnology: To be present in the scientifically most advanced regions of the country with the most lucrative market – the United States.

The interviews pointed into two different directions with regards to the importance of governmental support for their industry: Small companies emphasized the support provided by NIH and federal grant schemes such as the SBIR program. The closer a company comes to a marketable product the more predominant does the role of FDA as the ultimate arbiter of a company's fate in the market become. In between, federal policies impact access to capital, particularly venture capital and Intellectual property rights. These 'enabling policies' together are more important than the actual level of direct subsidies. Zooming in on these themes, the following chapters will therefore look into the neoliberal underpinnings of government interventions that helped the biotechnology industry flourishing. Specifically, chapter 5 will address policy mechanisms for the supply-side, such as research funding, patenting, technology transfer, venture capital financing, and regulatory approval. Chapter 6 will then describe how the American healthcare market with its unregulated prescription drug pricing came about and how the biotechnology industry, side by side with the pharmaceutical industry, has wielded political influence to keep it that way.

Chapter 5: The Invisible Hand of the Government

„*Es ist so schwer, den Anfang zu finden. Oder besser: Es ist schwer, am Anfang anzufangen. Und nicht (zu) versuchen, weiter zurückzugehen*."

(Ludwig Wittgenstein, Über Gewissheit, 1970)

5.1 Introduction

According to the VoC paradigm, the United States as a liberal market economy would provide a comparative institutional advantage for a rapidly innovating industry such as biotechnology. Such industries would profit from the shape of institutions of the political economy, such as the financial systems, the models of corporate governance, industrial relations, education and training, as well as inter-company relations. Yet the interviews in the previous chapter with biotechnology actors highlighted that the shape of these institutions does not capture the whole range of how institutional support structures for their business work. For example, biotechnology innovation is both creative destruction but also a very slow-moving process. Moreover, the clustering of finance and science, remains unaccounted for. At the same time, the interviews highlighted the importance of a number of 'enabling policies', government interventions that helped the biotechnology industry flourish.

This chapter will provide a historical perspective on key policy areas mentioned, such as funding for scientific research, technology transfer, patenting, venture financing, and

regulatory oversight. My aim is not to provide a complete chronological account of all the developments that may have contributed to the genesis of the biotechnology in the United States. Instead, I will highlight key political developments that created an institutional support structure conducive to a comparative advantage for the biotechnology industry in the United States. Looking at the evolving neoliberal regime that helped biotechnology innovation flourish in the United States, the chapter will confirm the claim that free-market rhetoric was regularly trumped by economic stimulus politics (claim 2).

I will therefore analyze the institutional support structure, the public groundwork, which private biotechnology actors willingly and ably exploit when claiming entrepreneurialism. I will argue that those actors – researchers, companies, universities, and investors - who were at the forefront of the scientific and technological developments of biotechnology could take advantage of a scientific infrastructure that was created over more than a century of United States' federal government policies. Although many of these policies had no direct impact on the substantive part of science and technology that is at the basis of contemporary biotechnology, they created the organizational and institutional foundation for the sciences to come.

Some history is therefore necessary to understand why and how the America's system of innovation was so susceptible to neoliberal reorganization that gained momentum by the late 1970s. The biotechnology industry came into being at this critical historical juncture as technological achievements coincided with the ascent of a neoliberal political and economic agenda. This agenda combined economic deregulation with a focus on the

supply-side of the economy. Support for developing and commercializing advanced technologies played a key role in this new agenda, which also comprised the provision of generous federal funding for public research; policies to allow its commercializing by private actors; the mobilization of new for-profit, private resources; and a general regulatory environment conducive to the needs of business. All this was not devised exclusively to benefit biotechnology, but it created an institutional comparative advantage for the biotechnology industry to flourish first and foremost in the United States. And, as chapter 2 illustrated**,** the long-lasting effect of this original comparative advantage is felt even today.

The chapter is structured as follows: To begin with, section 5.2 traces the evolving infrastructure for scientific research in the United States. Two developments led to an institutional comparative advantage for biotechnology in the United States: First, an ideology of 'making the peaks higher' has led to the clustering of scientific infrastructure. This organizational premise not only informed different waves of military build-up, but it also continues to be visible in today's geographic clustering of the biotechnology industry. Second, from its early beginnings, science and technology policies promoted entrepreneurialism among not-for profit institutions and scientists.

After World War II, the reconversion of these military resources for civilian purposes ushered in a division of labor, in which publicly funded basic research would be made available to for-profit actors who carried out applied research for commercialization. This setup also profited the development of biomedical sciences. Most important was the

evolution of the NIH into the world's largest organization for medical research, which will be tackled in section 5.3. The NIH not only increased the resources for biomedical research, it also institutionalized funding mechanisms based on peer review, which continued to allocate more resources to already existing clusters of excellence.

Eventually, the crisis of the post-World War II model of organization of the American society also reached science and technology. Although considerable federal resources continued to be directed to basic research, corporate actors complained that the state would become uncoupled from the needs of the private industry and its priorities for R&D. Section 5.4 therefore discusses the neoliberal turn of science and technology policies of the 1980s. To bolster American high-tech competitiveness various policies to accelerate development and commercialization of new technologies were devised. Legislation was adopted to encourage scientific entrepreneurs. As a result, patenting of federally funded research, as well as its out-licensing to the private sector were successfully taken up by biomedical researchers and corporate actors.

Moreover, the neoliberal preoccupation with the supply-side of the economy also benefitted biotechnology firms' never-ending need for capital. As a consequence of financial deregulation of the 1980s, new financial mechanisms were created that helped previously inaccessible funds to enter the speculative funding of high-technology ventures. Section 5.5 will address the policy changes that gave rise to these new financial vehicles, in particular the venture capital industry, as well as the evolution of stock market regulations.

An equally important regulatory issue for the biotechnology industry is the question of intellectual property protection. Section 5.6 investigates the importance and the *sui generis* character that the protection of intellectual property rights has enjoyed in the United States. Although patent laws have at times been lenient towards copying inventions, by the end of the 20th century the neoliberal paradigm considers strong patents inevitable to promote entrepreneurial activities. Specifically important for the biotechnology industry continues to be the issue of the patentable subject matter, as for instance organisms, tissues, and genetic information have not been easily subsumed under the logic of patent law. Ultimately, I will explain how the flexible, pragmatic, pro-commercialization approach of the American patent law turned out to be a key institutional comparative advantage for the biotechnology industry in the United States.

In a similar vein, from its early beginnings the United States' approach to regulate the safety of biotechnologies came down on the side of what is pragmatic and promotes commercialization. Section 5.7 will elaborate how, reacting to the first gene splicing experiments, a commercialization-friendly approach based on the product, not the process, became the yardstick for biotechnology regulation in the United States. This also provided a crucial comparative institutional advantage for producing and commercializing genetically modified crops in the United States first.

Yet the most crucial regulatory hurdle for launching products in the United States of the biotechnology and the pharmaceutical industry is the Food and Drug Administration (FDA). Section 5.8 will explain why the organization's history has not been without irony:

The FDA was challenged and underfunded by the neoliberal changes prescribed to federal bureaucracies by the Reagan administration. The agency had to endure until a new administration and Congress decided for an overhaul in the 1990s. I will discuss how reforms of the FDA administration streamlined the drug approval process in favor of the needs of the industry it was supposed to regulate. This transformation is also telling about a regulatory agency can turn from an impediment to an international comparative advantage.

Lastly, section 5.9 will conclude on the key aspects of the institutional support structure that profit the biotechnology industry in the United States. As the analysis has been mostly limited on the supply side, this section will also provide a segway to the next chapter, which will be tackling the influence of the United States healthcare system on the biotechnology industry.

5.2. Making the Peaks Higher

5.2.1 Early Beginnings that Count

From its first origins, the scientific infrastructure of the United States can best be characterized by its uneven geographic distribution of centers of excellence. This evolving infrastructure for scientific research in the United States could become an institutional comparative advantage for biotechnology in that country for two reasons: First, different waves of ‘making the peaks higher’ have led to the clustering of scientific infrastructure that continues to be visible also in today’s geographic clustering of the biotechnology industry. And second, from early-on science and technology policies promoted entrepreneurialism among not-for profit institutions and scientists. Rather than creating a

culture of knowledge for the sake of knowledge, this created a culture of science entrepreneurs that paved the way for their transition into a for-profit-mode when neoliberal supply-side policies encourage them to do so in the 1980s.

Historically, America's institutions of higher education evolved throughout several cycles of built-up: From the first elite colleges, all located on the East Coast, to educate gentlemen in the ways of theology, languages, and the classics; the Morrill Land Grant Act[47] of 1862 which granted each state federal land to use if for the establishment of a public college in the favor of agricultural and mechanical education; and the first designated research universities: In comparison with many European countries, the United States was considered to be a latecomer and before 1940 there were few areas in which American science was considered to be in the lead[48]. At that time, Germany's research universities had gained worldwide leadership in natural science. In the United States, the foundation of Johns Hopkins University, modeled after the German universities, was the breakthrough for a new kind of organization that allowed scientists to concentrate on their research rather than teaching. By the beginning of the twentieth century, there were fifteen universities that resembled today's blueprint for a research university: Johns Hopkins, Stanford and Chicago, which had been founded as research universities according to the German model; Ivy-League colleges such as Yale, Princeton, Penn, Harvard, and Columbia, which evolved into centers of scientific excellence; Massachusetts Institute of Technology (MIT) and Cornell, which developed as land-grant institutions; and state universities in Illinois, and in

[47] Public Law 37-108.
[48] For an overview of the history of the United States development in science and technology see Dupree (1986), Kleinman (1995), Mowery and Rosenberg (1993).

Michigan, Minnesota, Wisconsin and California, which had scientific and engineering research at their core (Crow and Tucker 2001). This distribution of centers of scientific excellence is noteworthy, because these research universities became the main recipients as a more structured funding for scientific and technological research evolved.

More than once this increase in funding dovetailed with a military build-up. The first watershed was World War I (Geiger 1986) because in addition to rallying more resources towards science and technology, it also established the practice of contract research, concentrated in a few research universities. This setup allowed scientists to remain at their home institution rather than work in a central government research facility (Kleinman 1995, p. 18). These trends were exacerbated by funding patterns established by philanthropic foundations, particularly those of the leading industrialists of the turn of the century, John D. Rockefeller and Andrew Carnegie. Initially, the philanthropic boost for science had been more a collateral of the general assistance to higher education. For example, in 1892 a gift of $800,000 by John D. Rockefeller single-handedly jumpstarted the University of Chicago. And while there was no direct links and strings attached to this support,

> "*it is important to note that even at this early date universities, and thus scientific research, were intimately linked to the economy, and the interests of universities were intimately tied to the fortunes of prominent capitalists.*" (Kleinman 1995, p. 28)

Over time, however, the focus of philanthropy shifted towards research. In 1902, Andrew Carnegie established the Carnegie Institution of Washington with a donation of $10 million. At that time, this sum was not only equal to Harvard's endowment it also surpassed the combined financial resources of all American universities that were dedicated specifically for research. Carnegie's new institution was set up to *"encourage investigation, research, and discovery"* by giving opportunities to the *"exceptional man"* with the aim to overcome America's *"national poverty in science"* and to *"change our position among nations"* (Kevles 1992, p. 195).

Philanthropic foundations established certain principles for the decades to come. In addition to contributing to the concentration of research in already superior institutions, foundations also contributed vast resources directly to science. Particularly the engagement of the Rockefeller Foundation to support selected fields that would directly contribute to the 'welfare of mankind' had a decisive impact on American physical and biological sciences. In the worlds of the Foundation's Board Member Wickliffe Rose, funding hat to be concentrated to *"[m]ake the peaks higher"* (Geiger 1986, p. 11).

When Rose's approach was taken over by Warren Weaver, who became Rockefeller Foundation's director of natural sciences in the early 1930s, this had two lasting consequences: First, Weaver's vision and the allocation of resources, particularly to the Californian Institute of Technology (Caltech), marshaled a paradigm shift in biological research by employing physical and chemical sciences, all of which ultimately coalesced in what was to become 'molecular biology'. This new research paradigm, investigating

biology on the molecular level, would later become the key to the commercialization of biological knowledge by the biotechnology industry (Kay 1993; Kevles 1992). Second, Rockefeller Foundation support reinforced already existing patterns of excellence for R&D and training in few, selected institutions profited universities such as Stanford University, MIT, Harvard, and Rockefeller University in New York. The ideology of 'making the peaks higher' created entities that have always had a business-oriented streak rather than a mandate to create 'knowledge for the sake of knowledge' (Kleinman, p. 36)[49].

Whereas the Rockefeller Foundation almost single-handedly remodeled the field of biology, the demands from 'big physics' could ultimately be met only by big government support (Kevles 1987, 1992). Federal engagement in science and technology was forever changed by the strong defense buildup during World War II, and particularly the research that was at the basis of the atomic bomb. The Manhattan Project to build an atomic bomb spent over $2 billion, employed many of the most eminent scientists and procured vast experimental production facilities from some of the nation's technologically most advanced companies. In addition to these expenses, the federal government spent another $2 billion on other military R&D (Hart 1998, p. 128). Throughout the years 1943-1945, more than 37 percent of the United States' GDP were spent for military purposes (Office of Management and Budget (OMB) 2009). The presence of such massive defense programs and the absence of a comparable civilian industrial R&D capacity had vast domestic consequences for the United States. It set the path for the distribution of wealth and power among its industry

[49] It is interesting to note that natural scientists never contended the increasing hierarchy among them. 'Making the peaks higher' in social sciences was later criticized as the 'Matthew Effect' by Robert Merton (1968).

sectors, classes, and regions, which later also had ramifications for the clustering of the biotechnology industry.

5.2.2 Science, the Endless Frontier After WWII

After World War II, a shift in research policy was intended to redirect the massive means for the military buildup toward civil ends. This was the core argument of the report "*Science – The Endless Frontier*" by Vannevar Bush (1945), who as director of the Office of Scientific Research and Development (OSRD) oversaw the Manhattan Project. Government science policies would have to be redirected to balance military security, public health, and economic welfare. Most prominently, the report featured the idea that also in times of peace, the promotion of science was indeed a proper concern for government. As the American government had always been engaged in the opening of frontiers – opening the seas to clippers and furnishing land to pioneers – it was within the American tradition that also the endless frontier of science should be made accessible by the federal government, because

> *"[t]here are areas of science in which the public interest is acute but which are likely to be cultivated inadequately if left without more support than will come from private sources. These areas – such as research on military problems, agriculture, housing, public health, certain medical research, and research involving expensive capital facilities beyond the capacity of private institutions – should be advanced by active Government support"* (Bush 1945, p.7).

When World War II came to an end, elite scientists under the leadership of Bush demanded that government guarantee its support for basic research, because this was the necessary foundation for a strong economy. Given the wartime success of military sciences, in particular the Manhattan Project, scientists' demand could muster vast support throughout society. Bush and his colleagues saw no need for government to fund applied or technology research, which they thought would put government into direct competition with industry. Conversely, private corporations were in favor of government funding for basic research, which was not profitable for firms who feared that 'free riders' would benefit from the research they funded (Kleinman 1995, p. 188). To some extent, this division of labor between the public and the private sector was indeed established. The quarter century after World War II was remembered by scientists as a 'golden era' of federal research funding, particularly after the lifting of the McCarthyite security restrictions in the middle of the 1950s:

> *"It was a time not only when money was freely available but when it was distributed in an apolitical manner and could be freely spent primarily in accord with* [scientists', VL] *professional judgement."* (Kevles 1992, p. 218).

How a-political research can indeed be is a legitimate cause for contestation. As long as there are more ideas than resources to pursue them, every priority chosen and resource allocated will be at the expense of foregone alternatives[50]. Yet after WWII, the federal

[50] In fact, there was also an alternative to Bush's policy prescriptions, promoted by Senator Harry Kilgore (D-West Virginia), who wanted a coordinated scientific agenda administered by a national science foundation. Agenda and foundation should be democratically accountable to a board composed of different societal stakeholders that included not only scientists, but also workers, business, and farmers. The purpose of

government did indeed become the prime patron for research and development. Towards this end, it also established an array of new institutions, such as the Atomic Energy Commission (AEC) in 1946; the various armed services agencies consolidated in the Department of Defense (DOD) in 1947; and the National Institutes of Health (NIH) in 1948 (see 5.3 below), which were an umbrella for the National Cancer Institute, the new National Heart Institute, as well as other research activities within the Public Health Service. A latecomer to this was the National Science Foundation (NSF), which was founded in 1950 to become the flag ship agency for basic research and training in all scientific disciplines. Yet at that time all biomedical research was already based under the guidance of the NIH, whereas virtually every other field of research was overshadowed by the various defense agencies (Kevles 1992, p. 212).

The Korean War quickly refocused the federal R&D agenda back to military needs. Defense spending rose to 14 percent of GDP in 1953 – the second-highest ever since WWII – and the DOD and AEC accounted for 80 to 90 percent of federal research monies. To a large extent military R&D expenditures went to those university campuses that were able to carry out basic research for military aims. This was the case, for instance, with MIT and its Research Laboratory in Electronics, which, at one point, had contracts with three different military agencies. Cold War research efforts were boosted again after 1957, when the launch of the Soviet Sputnik satellite triggered the creation of the National Aeronautics and Space Administration (NASA). As a consequence of the aerospace efforts, federal

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the science agenda was the promotion of economic wellbeing through applied research. According to Kleinman (1995), however, the fractioned American state, its parties, and the various informal rather than formal entry points into policy influence, ultimately tipped the balance in favor of elite scientific organization that would be geared towards basic research and administer itself.

research expenditures quadrupled until 1967. According to the rule of 'making the peaks higher' federal agencies' grants and contracts – again – disproportionately favored the most advanced research universities. This federal military R&D support compounded the already existing geographical and institutional concentration of a scientific infrastructure that contributed to the clustering of the contemporary biotechnology industry.

The state of California, which profited most from the different waves of military spending, demonstrates the lasting effect of these federal resource allocations. World War II changed the state from a resource-based economy into an advanced-technology economy heavily engaged in aircraft and battleship production. In 1963, California, with its large concentration of aerospace firms absorbed almost 39 percent of all federal grants and in 1980, over 44 percent of all NASA contracts and over 25 percent of all defense contracts were awarded to Californian firms (Fosler 1988, p. 211). Until Ronald Reagan became governor of California in 1966, the state allocated the extra tax revenues to public infrastructure programs, including colleges and its state university system[51]. These earlier investments paid off later thanks to the path-breaking research that took place there: For instance, at the University of San Francisco, Herbert Boyer, together with Stanley Cohen from Stanford University, developed the technology for recombinant DNA, which was patented and later commercialized by the first biotechnology firm, Genentech. Also the newly-built university campus of the University of San Diego has since played an important role for the biotechnology industry clustering around them. The relevance of the UC system for the biotechnology industry seems to be uninhibited by the fact that the state

[51] For an overview of these programs see Fosler (1988, pp. 214-220).

no longer prioritizes on higher education and by 2000 ranked only 42nd of all states in terms of general funding for education (Gittell and Sedgley 2000).

Again by the end of the late 1970s, heightened attention for national security led to an increase in federal R&D budgets. The largest share went to defense-related R&D, which in the late 1980s accounted for 70 percent of the entire federal R&D budget (Kevles 1992, p. 224). This increase in share was also the consequence of a relative decline in the budgets for non-defense purposes, such as health, the environment, natural resources, and energy. Moreover, due to the fear of international competition, particularly from Japan, the social utility of research was redefined as contributing to the country's high-tech competitiveness. For this, a closer cooperation between academia and industry was advocated, and later translated into specific policy measures for technology transfer and commercial exploitation of scientific research. This neoliberal turn in science and technology policies will be presented in detail in Section 5.5 below. Yet before it is first necessary to address the specific role of the NIH. Not only have the NIH been at the center of these neoliberal policy changes, but they are also the most important federal institutional support structure for most of the biomedical research that is finally commercialized by the biotechnology industry.

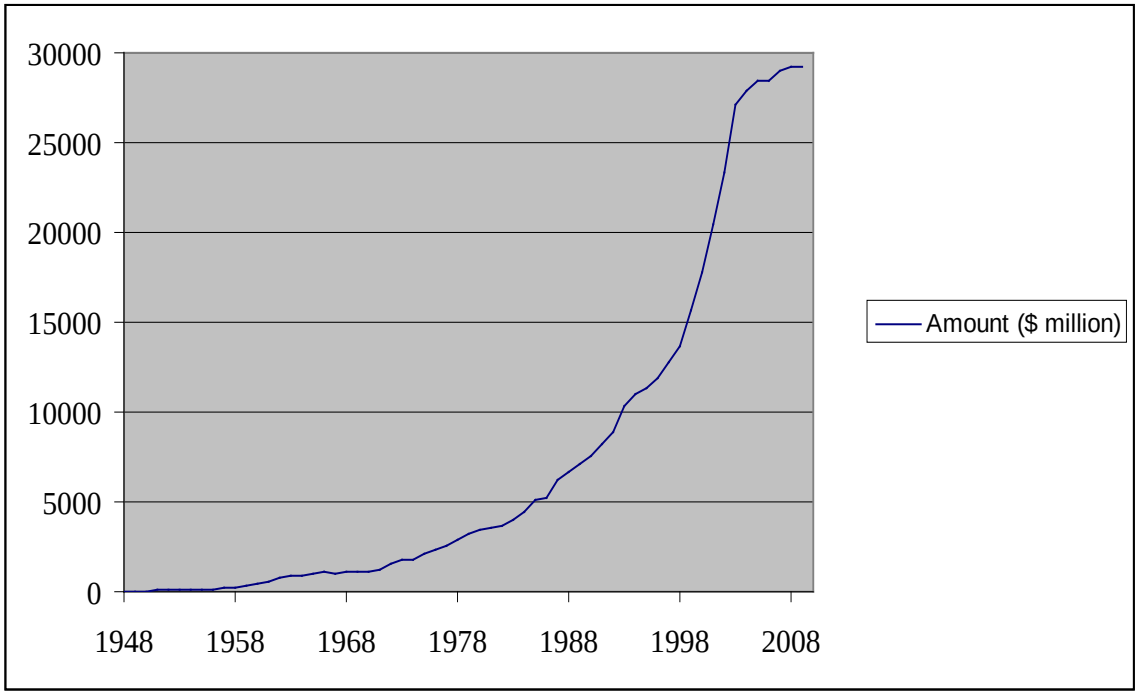
5.3 Federal Funding for Biomedical Research – The Role of the NIH

This recast of the history of the NIH illustrates on the one hand how this federal institution for health research has grown into a powerful system to stimulate and to fund basic biomedical research. On the other hand, NIH funding and support has continuously reinforced the clustering of biomedical research excellence.

The history of federal health research started in 1887 in a one-room laboratory within the Marine Hospital Service. This Hygienic Laboratory was turned into the (singular) National Institute of Health (NIH) by the Ransdell Act of 1930. Seven years later, the National Cancer Institute was founded and the then plural NIH became the umbrella that accommodated also later founded institutes such as those for research on mental health, dental diseases, and heart disease. From a small entity, which had only two research institutions and a budget of $25 million in 1948, the NIH grew steadily. The extension of funding for medical research channeled through the NIH was in part the consequence of competition with other agencies: Immediately after WWII, the NIH was able to have wartime contracts transferred to its jurisdiction. Moreover, as the American society prospered, elected officials noticed that appropriating funds for health-related research never lost them a vote. As a consequence, there were targeted ‘big government’ interventions to ‘go to war’ against certain diseases. Most prominently, Richard Nixon declared war on cancer and Congress passed a National Cancer Act in December 1971, as a consequence of which the NCI’s budget quadrupled over the next five years. Although

federal spending on the 'War on Cancer' amounted to over $50 billion so far, there are plausible arguments to see this war as a failure[52]. Yet these and other federally sponsored biomedical initiatives, such as the Human Genome Project, laid the groundwork for much of the contemporary biosciences. To date, the NIH has become a system of 27 research institutes and centers with an annual budget of $29 billion **(see Figure 5.1).** It is the most important public institution funding medical research, in fact the world's largest organization of its kind.

Figure 5.1: NIH Budgets Over Time



Source: NIH[53]

[52] A comprehensive account is presented by Goozner (2004).
[53] See http://www.nih.gov/about/almanac/appropriations/part2.htm

Moreover, the NIH also shaped the landscape for biomedical research because of the funding mechanisms it established. About 10 percent of the NIH's budget are spent on so-called intramural research conducted by scientists in the NIH's own laboratories, most of which are in Bethesda, Maryland. More importantly, 80 percent of the NIH resources are awarded through a competitive, peer-reviewed grant procedure to thousands of research groups throughout the United States. The NIH's grant-making function based on competitive peer review had the consequence that the competition urged researchers from early-on to obtain a business-like approach as funding cannot be taken for granted. Despite the level of competition – or rather, because of it - the best-equipped laboratories used to obtain the largest share of the grants. The allocation of NIH extramural resources has perpetuated already existing clustering of excellence in biomedical research: For example, from 1972 to 1981, a period during which a lot of the scientific basic research later commercialized by the biotechnology industry was generated, the top 20 institutions never received less that 51 percent of the total of extramural funds (National Institutes of Health 1981, p. 90). More recently, the NIH funds became disseminated somewhat more egalitarian. In 2005, when the NIH awarded a total of $23.4 billion to extramural research, the top 20 institutions received $7.3 billion in funding, or 31 percent (see Table 5.1).

Table 5.1: 2005 NIH Awards to All Institutions by Rank

Rank*	Organization	Number	Amount ($ million)
1	Johns Hopkins University	1299	607
2	University of Pennsylvania	1153	471
3	University of Washington	997	462
4	University of California San Francisco	988	452
5	Washington University	855	395
6	Duke University	795	391
7	University of Michigan	975	386
8	University of California Los Angeles	914	386
9	University of Pittsburgh	969	386
10	Yale University	868	337
11	Columbia University	763	331
12	SAIC-Frederick, Inc.*	1	328
13	Harvard University	682	321
14	University of California San Diego	681	309
15	Stanford University	763	306
16	University of North Carolina Chapel Hill	782	297
17	Massachusetts General Hospital	694	287
18	Case Western Reserve University	673	279
19	Vanderbilt University	668	266
20	University of Wisconsin Madison	670	257
	Top 20 Total:		**7,254**

*SAIC-Frederick, Inc. is a contractor that operates the government-owned laboratories at the NCI in Frederick, MD

Source: NIH http://report.nih.gov/award/trends/Rnk_05_All.xls, retrieved April 8, 2009.

On the other hand, looking at the geographical ranking of NIH award recipients, which was compiled for the last time in 2003, it seems that the old clusters of excellence, which dominated the allocation of resources for R&D already since World War I, continue to fare well. Research institutions and companies located in the five cities included in the interviews for this study, Boston, New York, La Jolla/San Diego, Baltimore, and San

Francisco, received more than $ 11 billion, 51 percent of a total of $ 21.6 billion of extramural funding in that year. **(Table 5.2)**: In this sense, the NIH continues to make higher the peaks of already existing excellence in biomedical research.

Table 5.2: NIH Domestic Institutions Awards City Ranking 2003

Rank	City	Number	Amount ($ million)
1	Boston	3,589	1,619
2	New York	2,989	1,218
3	La Jolla/San Diego	1,626	1,133
4	Philadelphia	2,014	804
5	Baltimore	1,831	764
6	Seattle	1,441	730
7	Los Angeles	1,422	606
8	Chicago	1,431	544
9	Houston	1,172	506
10	San Francisco	1,097	494

Source: NIH, http://report.nih.gov/award/trends/top100fy03.htm retrieved on April 8, 2009

Also the distribution of NIH funding to states fits into these well-established patterns:

Table 5.3: Leading States—Total of NIH Funding, FY 2007

Rank	State	Amount ($ million)
1	California	3,163
2	Massachusetts	2,236
3	New York	1,934
4	Pennsylvania	1,399
5	Texas	1,083
6	Maryland	976
7	North Carolina	931
8	Washington	786
9	Illinois	724
10	Ohio	628

Source: Battelle 2008, Table 18, p. 34

In sum, over the years the NIH has grown into a powerful system to stimulate and to fund basic biomedical research, which continues to favor many already existing clusters of excellence. The next section is dedicated to those neoliberal shifts in politics and policies that made biomedical research funded by the NIH or other federal grants ready for commercializing by biotechnology industry actors.

5.4 Neoliberal Policies Promoting Supply-Side Driven Technology Development

5.4.1 Abandoning the Post-War Consensus

Vannevar Bush's model for the Post-World War II division of labor in science and technology, assumed that the state was responsible for financing basic research, whereas private corporations were responsible for applied research and marketing. Yet this compact began showing its strains as early as in the mid 1960s, when corporate actors complained that state-funded research would become uncoupled from the needs of the private industry and its priorities for R&D. To counter this criticism, the Johnson Administration adopted the State Technical Services Act of 1965, which should accelerate technology transfer between laboratory and the market (Smith 1990, p. 59). More importantly, while for the most part of the post-World-War-II era, the United States' national investment on R&D was larger than those of all other OECD nations combined (Mowery and Rosenberg 1993, p. 29), subsequent administrations were confronted with a shrinking technological advantage between the United States and other industrialized countries, notably in Europe, and Japan. It seemed that creating military technologies, hoping they would spill over into civilian applications, was no longer a sufficient justification for federal research funding

and policies. Instead, to foster society's wellbeing as a whole, the United States innovation system, comprised of industry, universities, and federal government, had to change considerably.

By 1980, the approach towards science and technology was retooled with the overarching goal to strengthen the United States' military and economic competitiveness vis-à-vis other nations. In line with the rising neoliberal ideological paradigm shift, the newly elected government of President Reagan by no means advocated for a hands-off role of the state. Rather, the state's role was to provide a competitive advantage, to maximize the return on the nation's R&D investment, and to ensure the long-term viability of the country's science and technology base, on which private actors would then be able to capitalize. Against this backdrop, two policy initiatives turned out to be consequential: First, special funding programs for small innovative firms. Second, the transfer of technologies funded by those or other federal initiatives into the private sector. Both led to a remodeled, supply-side driven science and technology policy, which benefitted the unfolding of the United States medical biotechnology industry. And, as the interviews in the previous chapter highlighted, they continue to be relevant for the institutional advantage that biotechnology actors see the United States provide for their business also today.

5.4.2 Federal Funding for Small Businesses to Carry Out Innovative Research

The most important tool devised for channeling government monies into innovative, small firms was the Small Business Innovation Development Act of 1982[54]. The law requires

[54] Public Law 97-219.

federal institutes by law to set aside 2.5 percent of their extramural annual budget for a Small Business Innovation Research (SBIR) program. Since then, eleven federal departments and agencies, for example the Department of Agriculture, Department of Defense, and the Department of Health and Human Services, award a portion of their funds to small businesses to engage in R&D that has the potential for commercialization. To be eligible for an SBIR grant, businesses must be American-owned, independently operated, for-profit, and no bigger than 500 employees[55]. The purpose of the Act was to stimulate technological innovation; use small businesses to meet parts of federal R&D needs; and increase private sector commercialization of innovations derived from federal research (Gardner 1994, p. 39). SBIR programs comprise three phases: a first phase that currently grants $100,000 for a period of up to 6 months to carry out a feasibility study as to whether a proposed research effort could ultimately lead to a commercial product; a second phase with up to $ 500,000 for up to two years, if the continuation of the first phase is likely to result in a commercial product or service; and a third, final phase during which the research funded by government is commercialized with non-governmental monies.

SBIR grants are complemented by the Small Business Technology Transfer (STTR) program[56], which fosters public-private sector partnerships and joint venture opportunities for small business and the nation's premier nonprofit research institutions, such as colleges/universities, domestic nonprofit research organizations, and federally funded R&D

[55] Information retrieved on April 13, 2009 from U.S. Small Business Administration: http://www.sba.gov/SBIR/indexsbir-sttr.html

[56] The requirements for and the structure of STTR grants are similar to SBIR's, but STTR can provide more money (up to $750,000 for two years) in the second phase.

centers (FFRDCs)[57]. As many smaller companies interviewed pointed out in Chapter 3, theses federal grants often played a decisive role in moving a company forward. The most important federal institution for biomedical research, the NIH, disbursed 1811 such grants worth $626 million in 2008 alone. Moreover, this funding mechanism proves to be a reliable long-term opportunity available for small businesses to return to: over the last ten years, the NIH has granted over 18,000 awards worth almost $ 5.4 billion (Table 5.4).

Table 5.4: NIH SBIR and STTR Grants

Fiscal Year	Number of Awards	Award Amount (million $)
1999	1560	327
2000	1697	377
2001	1777	437
2002	1948	515
2003	2131	564
2004	2274	633
2005	2020	649
2006	1844	622
2007	1799	634
2008	1811	626
Total:	**18861**	**5,384**

Source: Table compiled by the author from NIH Office of Extramural Research website: http://report.nih.gov/reports.aspx?section=NIHFunding&title=Budget%20and%20Spending Retrieved April 8, 2009.

At the same time, the allocation of these grants continue to be distributed according to the patterns already established: Since 2000 California, Massachusetts, New York, and

[57] One example for such an FFRDC is SAIC-Frederick, Inc., (see Table 5.1 above), which is a contractor-operated government-owned laboratory at the NCI in Frederick, MD.
.

Maryland are always among the top five receiving states of SBIR grants, and since 1999 the top five states accounted for at least 49 percent of the total. (Table 5.5)

TABLE 5.5: NIH SBIR Funding by State (million $)

State	2008		2007		2006		2005		2004		2003		2002		2001		2000		1999	
	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank	US$	Rank
CA	103	1	100	1	106	1	108	1	113	1	106	1	90	1	75	1	58	2	55	1
MA	78	2	75	2	76	2	74	2	74	2	67	2	69	2	63	2	61	1	52	2
NY	32	3	31	4	24	4	30	4	27	4	29	4	25	4	18	4	16	4	12	5
MD	31	4	35	3	38	3	39	3	41	3	37	3	29	3	27	3	19	3	19	3
TX	26	5	29	5	19	6	27	5	24	5	19	7	15	7	13	7	13	6	10	6
PA	26	5	27	6	30	5	22	6	22	6	21	5	21	6	16	5	12	7	10	7
WA	20	7	18	7	18	7	19	7	20	7	21	5	22	5	15	6	14	5	17	4
Top 5	270		270		274		278		279		260		235		199		168		155	
Total SBIR	559		554		546		546		538		506		460		389		336		294	
Top 5 (%)	48.3		48.7		50.2		50.9		51.9		51.4		51.1		51.2		50.0		52.7	

Table compiled by author based on NIH data

Source: http://report.nih.gov/FileLink.aspx?rid=577 (retrieved April 30, 2009).

The SBIR/STTR program is an interesting case in point of how a neoliberal state plays a hands-on role in supply-side driven technological development: The underlying rationale for this program is threefold: first, similar to federally funded basic research, it supports R&D that may otherwise not be carried out. Second, and unlike basic research, it has a short-term focus with the endpoint of a marketable product being in sight in two and a half years. And third, it is structured as a competition between private businesses. In other words, the state finances private actors' applied research, but on a competitive basis that does not interfere with already existing markets.

5.4.3 Technology Transfer

By the late 1970s, in light of the shrinking technological advantage between the United States and other industrialized countries, debates in the United States broke out about how innovations were transferred between the federal government, universities, and industry. Whereas the United States' national investment on R&D continued to be larger than those of all other OECD nations, a substantial part of it was earmarked for creating military technologies. Yet these inventions no longer spilled over into civilian applications in a way that would safeguard the United States' economic competitiveness vis-à-vis other nations, notably Japan. Also for non-military purposes, political debates addressing science and technology asked whether in an increasing international competition the American society could afford waiting until the long-term benefits of federally funded basic research would disseminate into society quasi-automatically. Therefore, a turn of research and technology policies was advocated in which 'technology transfer' stood central. This term was coined to describe the systematic efforts to move knowledge from the public to the private sphere.

In other words: publicly created knowledge should be commercialized expeditiously by private actors, a process that continues to be central to the business rational of the biotechnology industry.

The most important milestone in this regard was the Patent and Trademark Law Amendments Act of 1980[58]. This bipartisan effort, more commonly known under the name of its two sponsoring senators Birch Bayh (D-Indiana) and Robert Dole (R-Kansas) stipulated that inventions made by academic scientists during federally-funded research were no longer the property of the government. Bayh-Dole established a uniform federal intellectual property policy that allowed universities, and other non-profit organizations, to reap the benefits from their federally funded research themselves. Institutions conducting research funded by federal monies became entitled to patent their discoveries, and to license them to investors and small business commercial partners. Since then, most American universities, certainly all relevant research universities, established a technology transfer office to engage in a multitude of commercializing activities. While research universities such as MIT and Stanford had been engaged in commercializing their research already earlier[59], patenting of academic biomedical research was still contested on ethical grounds. Until 1975, for instance, Harvard University had in place a policy that refused to profit from faculty research in public health and therapeutics (Smith Hughes 2001, p. 547). Yet as a consequence of Bayh-Dole, the number of patents issued by the PTO to

[58] Public Law 96-517.
[59] The oldest institution to patent university faculty's innovations and to commercialize them is the Wisconsin Alumni Research Foundation, which began in 1925.

universities alone has skyrocketed, from about 250 per year to more than 3,622 patents, 25 percent of which for therapeutic and biomedical inventions[60].

At its time, the Bayh-Dole Act passed uncontested. First, it was actually not all novel and contained many elements similar to previous efforts (Henderson and Smith 2002). And second, it was limited to small businesses and non-profit organizations, so that the Act was spared from opposition of consumer advocates or antitrust lawyers[61]. But the Act proved most consequential in the transformation of the division of labor between academia and industry without which also the ascent of the biotechnology industry would have been inconceivable. Bayh-Dole was the fire signal to bring publicly funded research into the fold of private commercialization, an endeavor whose magnitude unfolded throughout the coming years of 'Reagonomics'. The philosophy of the Reagan administration in this respect was summarized by President Reagan's science adviser, George Keyworth II, who contended that:

> *"most academic and federal scientists still operate in virtual isolation from the expertise of industry and from the experience, and guidance of the marketplace."* (Krimsky 2003, p. 30)

[60] Moreover, the technology transfer umbrella organization, the Association of University Technology Managers (AUTM), reported, that in 2007 their members had also granted 5,109 licenses and options signed and set up 555 startup companies (Tieckelmann, Kordal, and Bostrom 2007).

[61] Likewise, few took notice when on April 10, 1987, President Reagan's Executive Order 12591 lifted the ban for large corporations to profit from the Bayh Dole Act.

Consequently, the new administration issued a slew of new policy initiatives to overcome this perceived malpractice. In 1981, for example, the Economic Recovery Tax Act[62], a pre-eminent case of President Reagan's tax cut legislature, granted tax credits to companies that contributed research equipment to universities. Tax credits were also granted to Research and Development Limited Partnerships (RDLPs), (see 5.5 below), if these were established for the purpose of university-industry collaboration. In a similar vein, that year, the Office of Productivity, Technology and Innovation (OPTI) was established within the Department of Commerce. OPTI advocated the use of RDLPs at universities as a means of developing alternative sources of research capital and to limit their dependency from public funding. RDLPs should also accelerate the transfer and private appropriation – claiming of intellectual property – of federally developed and funded technology.

The first technology transfer law explicitly targeting federal research institutions was the Stevenson-Wydler Technology Innovation Act of 1980[63]. Its aim was to improve the utilization of federally funded technology developments in academia and in federal research institutions by state and local governments, and the private sector. The Act's Section 12 also stipulated the establishment of cooperative research centers between industry and universities, and the R&D collaboration between federal agencies and any of the government-operated federal laboratories with industrial organizations.

[62] Public Law 97-34.
[63] Public Law 96-480.

The Stevenson-Wydler Act, its amendment, the Federal Technology Transfer Act of 1986[64], and the National Competitiveness Technology Transfer Act of 1989[65] made technology transfer a mission of government-owned, contractor-operated (GOCO) laboratories and their employees. The legislation explicitly support that federally funded research be licensed to industrial partners. Particularly important, the heads of GOCO laboratories are authorized to sign Cooperative Research and Development Agreements (CRADAs). CRADAs are contractual arrangements that enable a federal laboratory or research institution to engage in a joint R&D effort with a private company. While federal agencies are prohibited from financing industrial counterparts directly, federal funds can be used to support a joint R&D infrastructure. CRADAs assign the rights to any intellectual property emanating from the joint research to the private company, while the federal government retains the non-exclusive right to license it back (Mowery 2003, p. 189).

Federal research laboratories, using CRADAs as a technology transfer mechanism, are coordinated under the Federal Laboratory Consortium for Technology Transfer (FLC). FLC is a nationwide network that provides the forum to develop strategies and opportunities for linking laboratory mission, technologies, and expertise with the marketplace. As of 2000, there were almost 3000 CRADAs (Mowery 2003, p. 191). Each federal agency and laboratory is free to develop its own CRADA model. Again, particularly relevant for biomedical research are the practices of the NIH and its laboratories.

[64] Public Law 99-502.
[65] Public Law 101-189.

Here, a controversy erupted that went right to the center of the problem of public funding for private profits. The reason was the so-called 'fair pricing' clauses of NIH CRADAs, which required corporate partners to put their 'reasonable profit' into a 'reasonable relationship' with the public's investment in it (Guston 1998, p. 236). Conflict initially arose over the anti-retroviral drug azidothymidine (AZT), which was launched in 1989 the United States by the pharmaceutical company Burroughs-Wellcome under the brand name Zidovudine. The public and particularly AIDS Activists were condemning the high price of $ 8,000 to 10,000 per year per person for a drug that was developed together with NIH researchers with public money[66]. Yet in 1995 the NIH director Harold Varmus decided to abandon reasonable pricing clauses in its CRADAs, because

> *"NIH's primary programmatic mission…is in biomedical research, not in product pricing."* (Rowe 1995).

Another set of tools emanated from the Omnibus Trade and Competitiveness Act of 1988[67] which, amongst other things, transformed the National Bureau of Standards into the National Institute of Science and Technology (NIST). NIST, which belongs to the Department of Commerce, obtained far-reaching authority to breach the division of labor between public and private research. Specifically, NIST began supporting directly companies' R&D as well as its commercialization.

[66] A similar conflict erupted around another CRADA between the National Cancer Institute and the company Bristol-Myers Squibb that led to development of the cancer drug taxol (Goozner 2004, p. 188).
[67] Public Law 100-148.

Towards this end, NIST established the Advanced Technology Program (ATP) to encourage companies invest in longer-term, high risk research with potentially high payoffs. ATP shares the costs for R&D with companies, thereby accelerating the development of early-stage, innovative technologies and helping companies raise their competitive potential. From 1990 until 2004, ATPs for biotechnology amounted to a total of $449 million (NIST 2004).

While CRADA and ATP were conceived to promote the United States' international competitiveness with respect to promising, future technologies, both policy initiatives also had the purpose to convert the federal large-scale scientific efforts from military to civil ends[68]. Biotechnology profited from this federal conversion strategy. In a similar vein, patenting reform measures such as the Bayh-Dole Act, were not explicitly conceived to promote biotechnology. Yet in combination they became effective just at the time when a second generation of start-up companies was ready to enter the market. Following the example of the successful university spin-off of Genentech of the 1970s, the second generation of university spin-offs created a boom of newly found biotechnology firms throughout the 1980s. This boom became possible only because of important changes that occurred with regards to the extension of capital for the industry, to which I will turn next, and the legal clarifications with regards to intellectual property protection, which will be addressed thereafter.

[68] Technology Access Report (1994), as quoted in Giesecke (2001, p. 191).

5.5 (De)Regulating the Provision of Capital

As biotechnology actors in the previous chapter highlighted time and again, most start-up firms require substantial capital beyond what founders can bring to the table or what the (normally loss-making) activities of the company generate endogenously (see 4.3). Yet firms that have only intangible assets, while looking ahead of years without profits are unlikely to receive a normal loan from a bank or another debt financing. Venture capital organizations finance such high-risk, potentially high-reward start-up companies and obtain a share in the company while it is still held privately. A generally agreed-upon definition of venture capital is that it is

> *"independently managed, dedicated pools of capital that focuses on equity or equity linked investments in privately held, high-growth companies"* (Lerner 2002, p. 327).

The VC industry was originally a purely American phenomenon that originated in the wealth management offices of business families such as the Rockefellers and Phipps. Yet the first genuine VC firm according to the abovementioned definition was established in 1946, when MIT President Carl Compton, Harvard Business School Professor Georges F. Doriot, and some local Massachusetts business leaders founded American Research and Development Corporation (ARDC). Capitalizing on their location and institutional affiliations, these first venture capitalists made high-risk investments into start-up companies that were founded on technologies developed for World War II. ARDC screened technologies from MIT for their potential to be developed into new, high-tech

business opportunities, recruited funds for them, and participated in their management. ARDC's largest success throughout its 26 years of existence was the $70,000 investment into Digital Equipment Corporation (DEC) in 1957, which was valued after DEC's IPO at $355 million. As institutional investors at that time hesitated to invest into such funds, ARDC was structured as a so-called closed-end fund that was marketed mostly to individuals.

One of the first steps that the United States government took to promote a professionally-managed venture capital industry was the passage of the Small Business Investment Act of 1958[69]. The 1958 Act provided venture capital firms structured as Small Business Investment Companies (SBICs) access to federal funds which could be leveraged against privately raised investment funds. Yet for two decades the annual flow of resources into these VC funds never exceeded a few hundred million dollars annually. Resources poured into VC increased by the end of the 1970s, as a consequence of a number of significant policy changes. Most important was a change in policy at the U.S. Department of Labor with regards to the Employment Retirement Income Security Act (ERISA). Through 1978, ERISA stipulated that pension managers invest with the care of a 'prudent man' and many fund managers abstained from investing in VC, because their engagement in early-stage companies could be conceived as imprudent. Yet in early 1979, the Labor Department ruled that an allocation of a small fraction of a portfolio to VC funds may very well be considered prudent (Gompers and Lerner 2004, p. 37). Consequently, from 1978 to 1983 the amount of VC invested increased from $414 million to $5,289 million and by 1986,

[69] Public Law 85-699.

pension fund provided for 52 percent of all contributions (Lerner 2002, p. 330). One other important change that contributed to this development was the rise of the limited partnership model as the dominant organizational form for VC funds. Limited partnerships do not pay capital gains taxes, only the investors to it are taxable. As pension funds and other non-taxable investors increased their contributions to VC funds, these funds themselves became exempted from paying taxes. These political changes that boosted the VC industry are emblematic for the paradigm shift toward supply-side economics: Instead of the state collecting revenues that could then be distributed to stimulate the demand-side of the economy, the state foregoes these revenues and leaves it over to the private sector to make a new stream of finance available for the supply-side of advanced technologies. Undoubtedly, throughout its history, the biotechnology industry profited from this paradigm shift.

Biotechnology firms' never-ending need for capital also led to the creation of new financial mechanisms, the most widely used of which became known as research and development limited partnership (RDLP), which was first invented by a Wall Street lawyer. In the early 1980s, as the biotechnology industry began taking off, RLDP's became popular among start-up companies to fund clinical trials or production scale-up. RDLP's helped startups to tap the capital of wealthy private individuals, which, in return for accepting the risk of their investment received royalties and stock options. Moreover, tax provisions allow these limited partners to obtain tax breaks, as their investment is considered R&D expenditure. Yet by the 1990s RDLPs lost their significance as a maturing biotechnology industry

needed even larger amounts of money, while at the same time new financial entities such as hedge funds allowed high-net-worth individuals even larger returns on their investment.

More important than RDLPs for the long-term development of the biotechnology industry – and the VC industry as its sponsor - was the existence of effective stock markets, which are regulated in the United States by the Securities and Exchange Commission (SEC). Whereas for a start-up company, the IPO at a stock exchange provides the opportunity to increase its capital base for future operations, for VC firms it is the preferred forum to recoup profitably their investment. Fledgling biotechnology start-up companies often times cannot comply with the requirements for revenues, profits, and cash flow that traditional stock markets impose on companies to be listed. This 'equity gap' is filled by the National Association of Securities Dealers Automated Quotations (NASDAQ). Originally established to trade in stocks that could not fulfill the rigid requirements of the American Stock Exchange (AMEX) and the New York Stock Exchange (NYSE), the NASDAQ turned into a fully computerized trading network in 1971 and is particularly used by technology startups. Also in Europe, fuelled by the technology boom of the 1990s, for instance in Germany a 'Neuer Markt' was launched in 1997 with the aim of matching NASDAQ as a stock market for innovative young companies. However, after losing 95 percent of its value, the 'Neuer Markt' was closed in 2002. The absence of a clear path towards liquidity was considered the key bottleneck for the development of a VC industry in Europe (Boquist and Dawson 2004). By contrast, the long-term availability of a trading floor for high-tech, high-risk companies turned out to be particularly relevant for the competitive advantage of the United States biotechnology industry in the long run. The

comparison between these different stock markets confirms the argument made by the VoC-approach: The structure of financial markets in the United States as a liberal market economy indeed provide a comparative institutional advantage that is crucial for high-tech, innovative industries.

5.6 Intellectual Property Protection

5.6.1 General Considerations Regarding Patenting

Whereas other forms of intellectual property right (IPR), such as trademarks and copyrights are relevant for other advanced industries, such as computer and information technologies, patents are the most relevant form of IPR for the biotechnology industry. According to Jasanoff (2005, pp. 203-4), patents played an indispensable foundational role in the development of the biotechnology industry, especially in the United States in three different ways: First, they created property rights for things that were previously outside of the realm for ownership claims. As a consequence, these newly commodified objects could be circulated and exchanged in markets. Second, since much of the early technological developments took place before there were any marketable, tangible products, patents provided the only evidence to investors that it was worth putting money into the fledgling technology. Third, patents created a guarantee that once there would be tangible outcomes and products, their commercialization would not be entangled in endless lawsuits. In sum, patents would order the increasingly complex web in which research subjects, researchers, universities, start-up firms, government and industry would engage to create and commercialize biotechnology.

In this vein, I will highlight two reasons why the U.S. patent system has turned out to be a comparative institutional advantage for biotechnology firms in the United States: First, the historic role that patent protection has played in the United States. And secondly, related, the ways in which the U.S. patent system was mended to combine the general logic of patents with the needs of biotechnology's new subject matter. Before these causes can be addressed, however, some general comments about the logic of patenting are necessary.

By granting a patent, an individual claim for inventiveness, it is assumed that this reward for an individual will trickle up and promote society's goods at large[70]. Patenting is therefore a reflection of the neoliberal creed to promote society's well-being at large by granting favors to individual economic actors. In theory, the idea of a patent is to reconcile the legitimate reward for an inventor's ingenuity with society's benefit from new inventions. Without patent laws, it has always been argued, inventors would either keep their innovations as secrets for themselves, or they would just not invent at all. By giving innovators for a limited period of time a monopoly on the economic exploitation of their invention, they would be rewarded and could recoup their investment. At the same time, society at large would profit from the disclosure of the invention. By granting an individual an exclusive property right, it is hoped that when these individuals pursue their own interest in a competitive market, the fruits of their labor would become accessible to the general population and would benefit society as a whole (Usselman and John 2006, p. 103).

[70] Such individualized view on knowledge production is by no means uncontested, as the vast body on the collective creation of traditional knowledge testifies. For an introduction see Shiva (1997); Sillitoe (2007).

Obviously, the functioning of IPRs would not be conceivable without the crucial role of the state: Claiming intellectual property only makes sense when there is an overarching authority that makes the rules and enforces them – if need be, even, internationally. The development of patents therefore is a story about the functioning of the neoliberal state. Moreover, a patent, like any other kind of intellectual property protection, is a historically constructed artifact. There is nothing pre-ordained about what should or should not be protected. On the contrary, by defining what constitutes intellectual property, particular perspectives are given the benefit at the expense of others, so that certain things become a property and others remain freely available (Sell and May 2001, p. 468). Seen this way, intellectual property rights congeal in a legalized way for a certain period the political struggles about technological progress. Such struggles reverberate throughout the history of the U.S. patent system. They are also the reason why an evolving view of patents has been of key importance for the development of the biotechnology industry.

5.6.2 The History of U.S. Patent Law

The evolution of the United States patent law is characterized by contingencies as well as contestations and contradictions. When looking at the history of intellectual property protection in the United States, three issues stand out that also reverberate in contemporary debates about biotechnology patents: *First*, there is the issue of *monopoly*. Over time, the balance between the interest of the public and the inventor has shifted back and forth and – as the case of patenting of DNA sequences demonstrates - continues to be a contested issue. *Second*, there is the question of relevance of patents for *trade*. The logical contradiction between the protection of intellectual property and the promotion of free

trade has made the United States government take different positions at different times, yet its interventions have regularly reverberated on the international and global level[71]. *Third,* there is the question of *what* can be patented. Problems pertaining to the subject matter for which patents could be granted had to be resolved and living matter, the object of biotechnological interventions, turned out to be particularly conflict-ridden.

The United States was among the first nations that developed a body of laws to protect the intellectual property of inventors. It is quite indicative of the industrious and economical nature of the newly-found nation that intellectual property rights were the only fundamental rights to be enshrined in the Constitution. Whereas rights such as free speech and freedom of religion, which were central to the debate of the framers, only amended the Constitution in a separate Bill of Rights, the U.S. Constitution, in Article 1 grants Congress the power

> "*to promote the Progress of Science and Useful Arts by Securing for limited Times the exclusive Right to their respective Writings and Discoveries*[72]*."*

The first United States Patent Law, adopted in 1790, was administered by Secretary of State Thomas Jefferson. And although this indicated the concern of the new government for the progress of sciences and technological inventions, relatively few patents were issued. In fact, at that stage of economic development, patents were detrimental for the young nation that was trying to catch up with a rapidly industrializing Europe. The United States' first Secretary of the Treasure, Alexander Hamilton, concerned himself with the

[71] This issue will be dealt with in detail in chapter 7 (see 7.5 below).

fledgling nation's dependence on manufactured British imports. Unlike many of his contemporaries who were informed by Adam Smith's classical liberal beliefs that manufacturers would grow in the just pace and size without government support, Hamilton's *"Report on the Subject of Manufactures"* (1817) drew up a mercantilist program to promote development of the domestic manufacturers. Government support for the economy, Hamilton argued, was not only necessary, but

> *"it is the right of every independent nation to pursue its own interest, in its own way"* (Hamilton as quoted in Ben-Atar (1995, p. 412)).[73]

Yet in the second half of the 19th century, changes occurred that altered the utility of a weak patent system for the United States: First, key technologies had become so complex that simply importing machinery and skilled workforce would no longer be sufficient to master a new technology (Chang 2001). Second, American companies started to obtain a competitive technological advantage over foreign companies (Sell 2003, p. 65). Corporations, such as the Edison Company, therefore lobbied the United States government to establish an internationally reciprocal patent regime that would allow companies to transfer their knowledge through an organized and enforceable licensing of patents. The second half of the 19th century, however, was an era of economic liberalism and intellectual property protection was seen at odds with the notion of free trade. Only in the aftermath of a global economic crisis of 1873 did the violation of free-market-

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[72] Constitution of the United States, article I, section 8, clause 8.

[73] Hamilton's adviser Tench Coxe even went one step further and came out publicly in favor of industrial piracy: if the British were reluctant to share their superior technologies with their former colony, then it was

principles become more palatable. As the protectionists won over free-traders in general, intellectual property was still considered a trade restriction, but this was no longer seen as a problem as long as it served the national interest (Sell and May 2001, p. 483). And internationally, the 1883 Paris Convention for the Protection of Industrial Property for the first time established transboundary rules and procedures for patenting.

Domestically in the United States, however, the push for patent protection became contested during the late 19th century. As a reaction to the increasing control of economic life through trusts, holdings, and other interlocking ownership structures, Congress passed several antitrust laws (Noble 1977, p. 88). While the Sherman Anti-Trust Act of 1890 proved to be mostly symbolic[74], the Act added to the general feeling that even if patents were monopolies only for a limited period of time, they were monopolies nonetheless and their benefits had to be justified (Kaplow 1984). Substantively more important towards limited patent protection was the passage of the Clayton Act of 1914, which forbade so-called tying clauses. Such tying clauses were a kind of a vertical restraint, which extended the reach of a patent on unpatented articles that are used in conjunction with a patented invention[75]. After the adoption of the Clayton Act, the Supreme Court subsequently struck down tying arrangements arguing that they were inconsistent with the overriding principle of free competition.

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time for the young nation to be creative about how to *"borrow some of their inventions"* (Coxe quoted in (Ben-Atar 1995, p. 396).

[74] The Act prohibited contracts, combinations, or conspiracies to establish monopolies in interstate or foreign commerce. Only eight law suits were instituted between 1890 and 1911, four of which were against labor unions. Moreover, it did nothing to prevent corporations from merging, which was exactly what happened at an unprecedented scale during that period.

[75] The Clayton Act was a reaction to the 1912 Supreme Court ruling *Henry v. A. B. Dick Co.* (224 U.S.1 (1912)), which stipulated that whoever bought A.B. Dick's patented mimeograph, had to purchase the

In fact, America's jurisprudence conceived of patents as monopolies for much of the twentieth century. Judicial attacks on the scope and validity of patents in addition to the enforced antitrust (anti-monopoly) legislation made American businesses rethink the economic value of patent protection (Sell and May 2001, p. 487). As a consequence, companies developed a cavalier approach towards infringing competitors' patents. For example, when the Eastman Kodak company in 1976 aimed at developing an instant camera to compete with Polaroid, Kodak issued an internal directive that

> *"[d]evelopment should not be constrained by what an individual feels is potential patent infringement"* (Silverstein 1991, p. 307).

The beginning of the 1980s marked a swing-back of the pendulum, once again as a combination of technological and ideological transformations. Advancements in fields such as information technology and biological sciences, as well as ideological shifts caused by the emphasis of private rights and property under the new Reagan administration, raised the importance of patent protection at the expense of free competition. As a consequence, important anti-trust stipulations were abandoned, such as the tying clause of the Clayton Act. The Act was increasingly considered as a serious impediment to America's international competitiveness, because it prohibited most forms of joint venture among firms in the same industry, which was felt to hinder intra-industry R&D joint ventures. Intense business lobbying efforts to remove this antitrust barrier and to increase national

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company's unpatented ink too, because it was "tied" to the use of a patented product through the use of a

competitiveness led to legislative changes stipulated by the National Cooperative Research Act[76] of 1984 (Barben 2007, p. 116).

Institutionally, the turn in favor of intellectual property protection was supported by the creation of the Court of Appeals for the Federal Circuit (CAFC) in 1982, a single 'patent court' that freed the overburdened court system from IP rulings. In the 1983 ruling for *Smith International v. Hughes Tools*[77], the Court heralded a paradigmatic shift by stipulating that public policy favors the protection of rights secured by valid patents and that public policy favors the innovator, not the copier (Kastriner 1991, pp. 13-14). Moreover, in 1986 the CAFC ruled in favor of Polaroid suing Kodak for infringing its patents for instant cameras. The ruling not only restored the company's monopoly over the United States market for instant photography, but in general it demonstrated that the time of cavalier patent infringements was no longer an economically viable option, because the costs for the infringer may run up to amounts that could wipe him out (ibid.).

American corporations took this as a sign that intellectual property was a system of protection, exclusion and opportunities for extraction of monopoly rents vis-à-vis competition and diffusion of knowledge. As technology-intensive industries increasingly stood the center of countries' competition with each other, patents and intellectual property

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licensing agreement.

[76] Public Law 98-462. With hindsight, given the current practice of biotechnology and pharmaceutical industry to invent around each others' patents, one of the reasons that business leaders brought to the public hearings is particularly interesting: The reform of antitrust laws to allow for R&D joint ventures was necessary because otherwise, unnecessary and wasteful duplication of research can hinder U.S. industries' ability to remain competitive in the world economy (Hemphill 1997).

[77] United States Court of Appeals, Federal Circuit - 718 F.2d 1573.

turned into a key concern at the juncture of trade with technology policies. Throughout the 1980s a paradigmatic redefinition took place, as a consequence of which patents were no longer considered to be hindering, but rather promoting free trade (Sell and May 2001, p. 489). This somewhat paradoxical logic argues that the liberalization of international trade requires the monopolization of what now becomes the most important factor of production: knowledge. It can best be understood as a neo-mercantilist turn: Unlike the old mercantilism that tried to shield domestic infant industries from external competition, the global protection of knowledge by intellectual property is a way to preserve the most advanced industries when they enter the competition in global markets (Bifani 1989).

Since the 1980s, therefore, United States' trade liberalization policies became intertwined with the protection of intellectual property rights. This nexus was at the core of the Uruguay round of multilateral trade negotiations, which ultimately led to a General Agreement on Tariffs and Trade and the establishment of the World Trade Organization (WTO) in 1992. The hallmark for biotechnology and pharmaceutical industries was the inclusion into the WTO establishment of an Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS was the result of a self-selected group of a dozen American firms[78], coordinating with like-minded companies from Europe and Japan in a 'trilateral group' and set out a blueprint for the TRIPS agreement, for which the United States trade negotiators successfully lobbied (Sell 1999).

[78] Coordinated in the Intellectual Property Committee (IPC) were Bristol Myers, CBS, Du Pont, General Electric, General Motors, Hewlett-Packard, IBM, Johnson & Johnson, Merck, Monsanto, and Pfizer.

5.6.3 Patentability Matters

Despite these international ideological drifts, in the United States the domestic legal basis for patent protection did not really change. Requirements for patentability are stipulated by the United States Patent Act of 1952[79], according to which patents have to meet four distinct requirements: First, the invention has to be of *patentable subject matter*. In other words, an innovation has to be 'a process, machine, manufacture, or composition of matter' (Section 101). Second, the invention had to be 'new'. The proof of '*novelty'* is based on the distinguishable claim with regards to other patents and already disclosed inventions at the time of invention (Section 102). Third, the invention must be 'useful'. This '*utility'* requirement implies that the invention has to show a working that renders some results. Finally, the invention must be '*non-obvious*'. This means that an invention cannot be patented if it is obvious to 'a person having ordinary skill in the art to which said subject matter pertains' (Section 103).

Questions of novelty, utility and non-obviousness have always troubled the courts and patent lawyers. By the end of the 1970s, however, the scientific and technological progress in biology required a clarification as to whether or not biological matters and processes are a patentable subject matter. A solution emerged through the court system after an employee of General Electric, Ananda Chakrabarty, construed a micro-organism through molecular (although not recombinant gene-splicing) techniques that was able to digest crude oil. Because of this feature, which is not found in any naturally occurring bacteria, the invention was believed to have significant potential for the treatment of oil spills and

[79] 35 U.S.C § (1952).

consequently, Chakrabarty filed a patent application. His claims were three-fold: First, on the process to produce the bacteria, second, on the way it is applied, and third, on the organism itself. The patent examiner allowed the first two, while rejecting the third claim, because micro-organisms are *"products of nature"* and, as living things, not patentable subject matter under U.S. patent law. Chakrabarty's appeal for patenting the organism was struck down by the Patent and Trademark Office (PTO) Board of Appeals, stipulating that laboratory-created micro-organisms are not products of nature, but as living things nonetheless exempt from patentability. Yet the next higher Court of Customs and Patents Appeal CCPA reversed the patent examiner's decision, contending that the mere fact that a bacteria is alive was without significance for the patent law. As the PTO appealed, the case was referred to the U.S. Supreme Court. In its 1980 landmark 5-4 decision *Diamond v. Chakrabarty*, the Court decided that man-made living organisms – in fact, *"everything under the sun that is made by man"* – was patentable subject matter. The Supreme Court pointed out that *"the relevant distinction"* established by the author of the patent law Thomas Jefferson (and later reaffirmed by Congress) in the Patent Act, *"was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions*[80]*."* While asserting the traditional distinction between nature and invention, the Supreme Court placed modified organisms such as Chakrabarty's bacteria in the sphere of the invention.

The ruling was of fundamental importance for biotechnology as it occurred at a time when the fledgling technology and industry strongly needed confirmation. In particular, it

[80] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), 313.

guaranteed investors to the young industry that their investments were matched, if not by products, but at least by some enforceable legal titles. *Diamond v. Chakrabarty* opened the door for the commercial applicability of biotechnology. But by treating the patentability of microorganisms as a purely technical issue that could be handled with the existing laws, the Court effectively closed another door before it was opened: The question namely, whether it should not be the task of Congress to assess the adequacy of the patent law in relations to new developments in the life sciences (Jasanoff 2005, p. 49). Moreover, the *Chakrabarty* decision became part of a larger regulatory regime specific to the United States, which from early on considers biotechnology and genetic engineering in terms of the *products* (which are patentable) and not in terms of the *processes* (which may bear risks), an issue that will be revisited in section 4.8.

The *Chakrabarty* verdict was not the only case in which imminent questions regarding the ownership of evolving technologies were depoliticized by leaving them over to the court system and its ruling on intellectual property protection. Another important case was *Moore v. Regents of the University of California* [81], which addressed the question whether a patient, who also happens to be a research subject, owns his own cells if they are turned into a research commodity. The claimant, John Moore, was a patient at the University of California in Los Angeles (UCLA) where he was undergoing treatment against leukemia. Without Moore's prior informed consent, two researchers established a cell line from his excised spleen, patented it and licensed it to a private company. The court ruled for Moore on the issue of the research physicians' financial duties and that research unrelated to a

[81] 51 Cal. 3d 134 (1990).

patient's health must be disclosed prior to the treatment. At the same time, however, the court denied Moore's ownership rights in his own cells. These cells, according to the court, were not unique, whereas the extraction of proteins from these cells was unique enough to grant the researchers a patent. According to the court ruling, granting property rights to the human sources of biological material would introduce uncertainties that could be detrimental to academic research. Instead, the ruling introduced certainties with regards to the division of rights: informational rights for the patient and property rights for the researcher (Jasanoff 2005, p. 215). As a consequence, this pragmatic compromise fit comfortably with the imperatives of neoliberal economic thinking: Fostering entrepreneurship that leads to product innovation was a desirable outcome in its own right, even if it infringed on other rights, such as the undivided autonomous ownership of an individual over his/her body.

Subsequently, a whole new range of opportunities for commodification by means of intellectual property rights arose when biological techniques moved from the cellular down to the molecular level. Whereas the above cases, or the patenting of transgenic animals such as the infamous Harvard Oncomouse[82], created a public stir, the patenting of human DNA sequences that started by the 1980s was hardly noticed. Initially the PTO treated DNA sequences as chemicals (Eisenberg 2006) and the scientific community did not oppose this patenting of DNA sequences until 1991.

[82] For an overview of the public and patent stirs around the most litigated mouse in history see Blaug et. al (2004).

Then, at the beginning of the Human Genome Project, NIH researchers in the laboratory of a certain J. Craig Venter filed for patent applications on several hundred DNA fragments. These fragments, known as complementary DNAs (cDNAs) or 'expressed sequence tags' (ESTs), are parts of the DNA's nucleotide sequence that become visible when a gene is translated into a protein, which in itself does not say anything about the function.

Many scientists, including James Watson who was then the director of the NIH's genome program, objected on principle to the patentability of such partial genetic information. At the same time, the biotechnology industry was split. Some companies endorsed the NIH's patents on ESTs as long as the federal agency would not favor any one company over another with licensing agreements. Yet others contended that the government must not control a product to whose development it has contributed little. For example, the Pharmaceutical Manufacturers Association contended that government devising policies with regards to ownership and licensing of gene sequences would inevitably be detrimental for R&D of new medicines in this country (Eisenberg 1992). In both cases, therefore, the contention was not ownership of these sequences *per se* but ownership or control *by the government*.

The mounting controversy was temporarily defused when in August 1992 the PTO rejected the Venter/NIH claims because they failed to meet the standards for non-obviousness and novelty. Subsequently, in February 1994, under its new director Harold Varmus, the NIH declared to withdraw all patent applications on ESTs, which by that time had multiplied to almost 2,700. In the event, Watson resigned from the NIH in 1992, in part because of the

NIH's continuing efforts to patent ESTs (Kevles and Berkowitz 2001), whereas, also in 1992, Venter left to head the new Institute for Genomic Research with a corporate partner, Human Genome Sciences (HGS). HGS, like Venter's next company, Celera, founded in 1998, upped the ante and filed patents for thousands of ESTs. Although their function was unknown, throughout the 1990s the PTO considered these sequences patentable because they would meet the criteria of novelty and of utility as biochemical probes or generally as research tools. Hence, genomics companies such as HGS, Celera, Incyte, and others, filed thousands of patents on sequences of unknown function.

Tension rose again when Celera and other companies announced to use ESTs to identify new genes, extrapolate their function through computerized searches for functions of genes with similar structure in already publicly available databases of the Human Genome Project, and claim utility patents for their 'new' genes. One counter-reaction from corporate actors interested in commercializing gene-sequence related technologies was the establishment of the SNP Consortium (see 2.6 above). On the other hand, also the international biomedical research community became increasingly uneasy about the drive towards commodification of the human genome. In March 2000, Aaron Klug and Bruce Alberts, the presidents of, respectively, the Royal Society of London and the National Academy of Sciences in the United States, publicly declared that guessing gene functions by computerized searches of genomic databases was a trivial matter that may satisfy current shareholders' interest, but did not serve society well. Emphasizing that these results would not warrant patent protection, they demanded that *"the human genome itself must be freely available to all humankind."* (Alberts and Klug 2000). Their statement was

orchestrated in conjunction with a joint declaration by U.S. President Clinton and U.K. Prime Minister Tony Blair in March 2000, who agreed to move data from the Human Genome Project as quickly as possible into the public domain.

Efforts of the scientific community and changes in political climate eventually pushed the PTO to specify its position on the patentability of gene fragments. In January 2001, the PTO issued new guidelines according to which patents would be issued only for sequences that are used in identifying structures of predicted biological function (U.S. Patent And Trademark Office (USPTO) 2001). While this decision still allows for a very broad understanding of what types of DNA sequences can be patented, it reversed a practice of companies filing for a patent as soon as an EST was sequenced. Subsequent EST patent applications were rejected by the PTO and rejections were upheld before the CAFC. Many of the old patent applications, if challenged, would most likely not meet the new thresholds for utility and may therefore have been abandoned (Davis et al. 2005). And while a recent study indicated that nearly 20 percent of human genes were associated with at least one U.S. patent (Jensen and Murray 2005), there is evidence that the number of patents being applied for and granted peaked between 2001 and 2002 and is declining ever since (Hopkins et al. 2007).

How should these developments be interpreted? The legalistic reading of them argues that these rulings are part of a broader, general change in patent law that took place since the *Chakrabarty* decision: The Federal Circuit started granting patents to subject matters previously not patentable, such as business methods and mathematical algorithms. Like

them, gene sequences of known biological structure and functions are now considered as inventions that become patentable as long as they are 'useful' (Eisenberg 2006)[83]. My own, political reading is that these changes in patent law reveal much about the increasingly complicated tasks that the neoliberal state has to play. The rules of law should establish a level-playing field for the competition among private actors pursuing their economic self-interest in the hope that this will promote society's well-being at large. This balance is politically contested and requires periodical readjustment. For example, the state may have to intervene when some private actors' pursuit of economic self-interest became too successful so that it threatens to block off the development of certain goods that are deemed economically pre-competitive. This was the political reason to keep the sequence of the human genome public. Another reason for intervention may be that different groupings of important private actors are at loggerheads. This was the case in a recent Supreme Court ruling[84] that pitted the pharmaceutical industry against the computer industry. Court rulings are less politicized and generate less friction than for instance legislative means to settle these discrepancies. They can therefore be updated faster to keep pace with technological advancements, which is an institutional comparative advantage for the United States and its biotechnology industry.

[83] The economic reading of what 'useful' means was highlighted in chapter 4: Many genomics companies saw the value of their genetic information depreciating after it turned out that the way from a gene to a commercial product – in most cases a drug – was much more complicated and lengthy than initially hoped.
[84] KSR v. Teleflex, 550 U.S. 398 (2007). The Court came down on the side of the computer industry and decided that the combination of two existing technologies was too obvious for enjoying patent protection. Such follow-up patenting is a common practice for pharmaceutical – and biotechnology companies, which often seek new patents for minor modifications to existing inventions, such as combining two medicines with another (Patently Obvious: America's Supreme Court Raises the Bar for What Deserves a Patent 2007).

The United States patent system seems to have a comparative advantage relevant for biotechnology actors on at least two other accounts: First, there is evidence that patents in the United States are considerably cheaper than in other advanced capitalist economies[85]. Second, a patent in the United States becomes publicly revealed not at the point of its filing, but only when it is granted, which may be many years later. This way, companies do not have to disclose their technological advancements, but can instead file strategic patents around their inventions that create roadblocks for their competitors[86]. Given these advantages, it is therefore no surprise that the United States remains the country with the highest activity of patent claims relevant for the biotechnology industry[87].

In conclusion, patent laws are an example for how neoliberal ideology of state intervention for market-based solutions is put into practice. The evolution of the U.S. patenting framework became part of the comparative institutional advantage that set the scene for an early commercialization of biotechnologies in this country. Following a similar line of inquiry, the next section will analyze the overall regulatory framework for biotechnology in the United States. Specifically, it will be analyzed what steps the government in the United States undertook – or not – to regulate new biotechnologies, and whether or not this contributed to the country's comparative institutional advantage.

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[85] According to the OECD, a patent in the United States costs € 10,330, compared with € 49,900 in the European Union costs and € 16,450 in Japan (Lawrence 2008).

[86] One strategy that generates sea mines rather than roadblocks pursies so-called 'submarine patents': Companies secretly file a patent application and keep it pending until another company invests heavily in the same technology. Then, if the patent is brought to be issued, the investing company is forced to either redesign its product or pay licensing fees to the patentee.

[87] A recent analysis of some 15,000 patent families claiming human DNA sequences showed that if one or more patents were granted, 94 percent of the cases were coming from the USPTO, whereas the European and the Japanese patent authorities granted only 5 and 3 percent respectively (Hopkins et al. 2007).

5.7 Regulating Biotechnology in the United States

Similar to the adaptations of the patenting laws, also the regulatory process had to catch up with the progress made in biological sciences: Shortly after Stanley Cohen and Herbert Boyer, together with others, published their path-breaking article about the transfer of DNA between species (Cohen et al. 1973), scientists themselves asked whether these techniques bore a hazardous potential that had to be curbed. As a consequence, the National Academy of Sciences asked one of the pioneers of biomolecular research, Paul Berg, to lead a study committee for potential biohazards. The eleven elite scientists, all of which had already been actively involved in the field, published a report in 1974, which is generally considered to be the starting point for public debates about genetic engineering[88]. The Berg Report called for a voluntary moratorium of research until certain types of hazardous risks were better understood and precautionary measures designed to prevent them (Berg 1974).

While this one-time and exceptional moratorium lasted for only about half a year, it sparked increasing global awareness about the need to regulate this new field of biological sciences. The issue was revisited in February 1975 at a conference in Asilomar, CA. This meeting of U.S. and foreign scientists, sponsored by the NIH, the NAS and the NSF, allowed a self-selected academic avant-garde – thereby excluding other social actors – to define risk in their own terms. In Asilomar it was agreed to substitute the memorandum with a first framework of regulatory principles based upon which research should progress. As could be expected from a meeting of biologists, the problems and solutions they

[88] For an overview of the early days of the debate about regulation of genetic engineering see Krimsky (1982).

formulated were kept on a technical level. Moreover, despite the international participation, there was no doubt that the leading role – given the state of scientific affairs – had to be played by United States agencies. And since the NIH was the world's leading governmental biomedical research sponsor, it was the logical institution for governmental oversight. Consequently, in June 1976 the NIH issued its 'Recombinant DNA Research Guidelines', by which the United States became the first country to establish a regulatory framework for recombinant DNA research (Gottweis 1998, p. 91). The NIH, familiar with control of scientists by scientists through a peer review process, established an interdisciplinary Recombinant DNA Advisory Committee (RAC). The RAC, which only later included also non-biologists, in fact almost immediately gave a go-ahead sign, because the NIH, in the words of its then director Donald Fredickson, felt that

> *"[t]he additional hazards are speculative and therefore not quantifiable. In a real sense they are considerably less certain than are the benefits now clearly derivable from the projected research."* (U.S. Department of Health 1976, p. 27904)

In other words, benefits were certain, risks were not. This belief informed the first regulatory framework, which contained a number of characteristics that turned out to be decisive for the path that biotechnology took in the United States: To begin with, as the U.S. was the first country to have such framework, this provided a first-mover advantage for research located in the United States. Also, the guideline was devised by the NIH for

federally funded researchers, but not for those from the private sector[89]. The private sector could participate in a voluntary compliance program, to preempt eventual future public concerns (Barben 2007, p. 181). Most importantly, regulation remained to be a technocratic act of scientists for scientists: In the late 1970s, a number of bills were introduced in Congress to provide a guideline for biotechnology research and address its hazardous potential. These efforts came to a halt with the failed initiative of Senator Stevenson (D-Illinois) in 1980. As a result, in the United States biotechnological research unfolded within a regulatory framework that has not been set up by elected officials, neither did it take seriously into account opinions others than those of the research community (Krimsky 1982). What this meant in practice was that the NIH handled its guidelines in a flexible, cooperative manner. This allowed the organizations and scientists that carried out recombinant DNA research to request lighter regulation as science progressed. As a result, already in 1978 the NIH guidelines were substantially loosened by vastly extending the experiments for which no registration was necessary.

But as technological progress gained further momentum, the NIH-RAC review process ultimately turned out to hinder the commercialization of biotechnologies[90].

[89] This division of regulation continues until today and is part of the current debate about stem cell research (see 7.3 below).

[90] One highly contentious case was of a genetically modified anti-icing bacterium that would increase the frost resistance of commercial crops such as strawberries. The RAC's decision that such bacteria were safe was overturned by a federal court of appeals on the ground that the NIH had not carried out the necessary environmental impact assessment (See *Foundation on Economic Trends v. Heckler*, 756 F.2d 143 (D.C. Cir, 1985).

devised a ‘Coordinated Framework for the Regulation of Biotechnology’ that redistributed the responsibility for articulating and enforcing regulation among three different federal agencies (Jasanoff 2005, pp. 51-52): The Environmental Protection Agency (EPA) became responsible for environmental applications and impacts, including pesticides; the FDA for new foods, animal drugs, and pharmaceuticals; and the USDA for new crops and animals. For policy purposes, biotechnology was henceforth considered as just another industrial process that supplied familiar classes of products. Merely using rDNA techniques, which so far were lacking any known hazardous attributes or consequences, would not make a harmless product dangerous. By executive order it was decided that regulation of biotechnologies should rely on existing laws applied in familiar types of reviews carried out by already established agencies. In other words, the institutional setup already at hand was considered to be sufficient to control also any new risks that the new classes of biotechnological products may bring about.

The general assessment of the technologies based on product, not the process, was reiterated by a high-level report of the National Research Council (National Research Council 1989). It added considerable authority to a narrow regulatory framing in the interest of those who aimed for an expeditious commercialization of the new technologies. By narrowing down the perception of risk, the regulatory framework yielded a competitive advantage over Europe, where in many countries, as well as on the level of the European

Union, rDNA risk assessment and regulation continues to be a matter of risks of the process[91].

My study does not address the agricultural applications of biotechnology[92], where the United States' lenient and accepting regulatory framework provided a comparative institutional advantage crucial for the large-scale introduction of genetically modified, and commercially valuable crops, such as corn, soybean, cotton, and tomato[93]. As highlighted by the interviews in the previous chapter, the crucial regulatory agency for biotechnology's medical applications is the FDA, to which I will therefore turn next.

5.8 The Regulatory Approval by the FDA

As mentioned above, the U.S. regulatory regime towards biotechnologies and genetic engineering is based on the evaluation of the product and not the process. Hence, drugs that are produced by recombinant DNA techniques follow the pathway towards regulatory approval similar to conventional chemically synthesized drugs. The following account of the FDA's role therefore does not distinguish between the origins of the drug but focuses on the agency's internal mechanisms and the external political pressures.

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[91] For an historic overview of the evolving European regulatory policies see (Gottweis 1998, pp. 105-152). This different interpretation of risk also made genetically modified crops an unresolved trade conflict issue. In May 2002, the Bush Administration initiated action at the World Trade Organization (WTO) against the European Union's (EU) moratorium, or freeze, on genetically modified organisms (GMOs), arguing that the E.U.'s moratorium was illegal, non-science-based and *"harmful to agriculture and the developing world."*(U.S. Trade Representative 2003).

[92] For an overview of the political economy of agricultural biotechnology see (Pistorius and van Wijk 1999).

[93] In 2008, the United States grew about as much GMO crops, 62.5 million hectares, as the rest of the world combined. See http://www.isaaa.org/resources/publications/briefs/39/pptslides/default.html, retrieved 4/21/2009.

To date, the FDA is in charge of regulating a number of products other than drugs[94]. As the FDA regulates a broad range of industries – from small biotechnology firms over pharmaceutical companies and food corporations – it has been estimated that the agency regulates products accounting for about 20 to 25 percent of every dollar spent by U.S. consumers (Ceccoli 2004, p. 4). The agency regulates food-related products such as dietary supplements; medical devices such as pacemakers; biologics such as vaccines and blood products; animal feed and drugs; cosmetics; and radiation-emitting products such as cell phones. By their very nature, many of these products belong to the most heavily regulated items on the market. While this is hardly a sign for unfettered competition so dear to market-led ideals, this section describes how principles of deregulation nevertheless held sway at the FDA. As a consequence, the FDA underwent changes that streamlined its procedures for drug approval to bring them more in line with the needs of the industry that it regulates. Unlike the sea-change that occurred thanks to supply-side economic policies throughout the 1980s, the neoliberal turn at the FDA occurred only by the 1990s.

From Aspirin to Zoloft, to date the FDA acts as the gatekeeper determining what drugs become legally available in the United States[95]. The core of the FDA's business is the approval of new molecular entities (NMEs), which refers to any drug that has active ingredients that have never been approved for application in the United States. In addition to approving NMEs, the FDA also handles the new or expanded use of an already approved drug for another medical indication, or supplementary substances that may enhance the

[94] This section draws on the historical account provided by Ceccoli (2004).
[95] The consequences of this gatekeeper function cannot be overestimated. As the case of the cancer drug Erbitux that was developed by the biotechnology company ImClone demonstrated (Ceccoli 2004 p. 9),

efficacy of already existing products. Throughout its history the FDA underwent several administrative reorganizations as well as name changes. Yet its mission has always contained the two components of law enforcement and consumer protection. As early as 1880, the federal government and the Department of Agriculture's Division of Chemistry started to concern themselves with the purity of foods and drugs. USDA's Bureau of Chemistry had the mandate to protect consumers from fraudulent, impure, or mislabeled substances. The mandate was enshrined in Congress's Pure Food and Drug Act of 1906[96], but gained little regulatory traction[97]. Several administrative changes led to the renaming of the agency as Food and Drug Administration in 1931. More importantly, in the 1930s a marketed product, the so-called Elixir Sulfamilamide, turned out to be a toxic substance that killed more than 100 Americans, thereby exposing the weaknesses of the existing drug legislation. This was rectified by the Food, Drug and Cosmetic Act (FDCA) adopted in 1938, which established a centralized regulatory apparatus. The Act for the first time required pharmaceutical manufacturers to demonstrate to the FDA the safety of their products prior to commercialization.

Sparked by another medical incident, this time mainly in Europe, where the side effects of a sleeping pill based on the substance thalidomide led to limb deformities in newborns, the FDA's role in overseeing drug approval was strengthened by the so-called Kefauver amendments in 1962. The sponsor, Senator Estes Kefauver (D-Tennessee), initially

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declining regulatory approval for a specific drug can send the entire industry into a tailspin, taking down investors, insider traders, and even home improvement icon Martha Stuart.

[96] Public Law 59-384.

[97] Also in 1906, Upton Sinclair's book "The Jungle" created a public outcry about the meat processing industry. Because the production and distribution of food increasingly turned into a large-scale, industrialized

concerned himself less with safety but more with the profits that drug companies could accrue throughout the 1940s and 50s, when the ‘therapeutic revolution’ and the ‘golden age of drug discovery’ led to a plethora of new drugs (see 2.3). Yet as part of the bargaining process that ultimately led to its adoption, the 1962 Amendment lacked drug pricing provisions (Ceccoli 2004, p. 76). But the amendment had far-reaching consequences in other ways, as it required from drug companies a ‘proof of efficacy’ in clinical trials to demonstrate the drug’s effectiveness according to the claims of the manufacturer. Moreover, the amendments also devised a mandatory, multi-tiered approach for drug approval: First, a so-called investigational new drug (IND) application prior to the clinical testing on humans. Second, the so-called new drug application (NDA). Only afterward could a new drug be marketed to the general public. In sum, the regulatory authority and responsibility of the FDA became strengthened (Ceccoli 2004 pp. 78-79). The FDA was also authorized to develop its own efficacy standards based on substantial evidence, which were codified in the Code of Federal Regulations (CFR) in 1969. These efficacy standards stipulate that there have to be at least two well-controlled clinical trials plus one confirmatory trial to establish efficacy and trial designs including the use of blinded studies, randomization, and placebo controls. Ever since, the regulatory approval of a new drug consists of a preclinical testing, three different clinical tests and a post-approval testing (Table 5.6).

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business, consumers increasingly became reliant upon a system of testing and quality approval. Science became necessary to establish standards for regulation and its enforcement (Dupree 1986, p. 177)).

Table 5.6: The FDA Drug Approval Process

	Clinical Trials					
	Preclinical Testing	**Phase I**	**Phase II**	**Phase III**	**FDA Review**	**Phase IV**
Years	3.5	1	2	3	1*	
Test Population	Laboratory and animal studies	20-80 healthy volunteers	100-300 patient volunteers	1,000-3,000 patient volunteers	Review and approval process	
Purpose	Assess safety and biological activity	Determine Safety and dosage	Evaluate effectiveness and side effects	Verify effectiveness; monitor long-term effects		Post-marketing testing
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved	

*Median review period for regular applications in 2005, according to US FDA (2006).

Adapted by the author from Wierenga and Beary (1995).

As the entire approval process can easily span an entire decade, the requirements have become contested by industry representatives and their acolytes as an impediment to introducing new drugs. Enhanced safety provisions and the centralized regulatory restriction of FDA approval were criticized to create a slowdown in drug approval that generated a ‘drug lag’ in the United States relative to other countries. On the other hand, the former FDA Commissioner Donald Kennedy argued that ‘drug lag’ was a global phenomenon. After the 1940s and 50s were bringing the ‘low hanging fruits’ of drug development to the market, the basic knowledge in the industry was exhausted by the industry by the 1960s (Kennedy 1978). Yet free market advocates, such as researchers and policy analysts affiliated with the American Enterprise Institute (AEI) fuelled the debate with a number of studies that argued that regulatory delays created a serious hindrance for

both pharmaceutical innovation and public health[98]. These concerns resonated well with the increasingly anti-regulatory *zeitgeist* of the 1980s, and Congress, which was initially mixed, picked up this criticism in the 1980s, chastising the agency for moving too slowly (Ceccoli 2004, p. 93). In fact, the agency was urged to do more with less. While appropriations to the FDA had increased throughout the 1970s, they began leveling off through the mid 1980s when the Reagan administration downsized the federal bureaucracy. Reagan included in his 1985 budget proposal that the FDA levy user fees on the industry. However, as he wanted to use the money to reduce the deficit in the federal budget rather than increasing the agency's regulatory capacities, the proposal could not muster support from either industry or Congress and ultimately failed (Ceccoli, p. 109). Last but not least, patient organizations, particularly AIDS activist groups such as ACT Up, increasingly urged the authorities to expedite their procedures and legalize experimental drugs for treating life-threatening illnesses[99].

A new regulatory period started with the adoption of the Prescription Drug User Fee Act (PDUFA)[100] in 1992, which modified the drug approval process in significant ways. First, administrative changes allowed for a fast-track approval of experimental drugs to expedite the development of new medicines. Second, Congress made the future appropriations of the agency dependent on meeting certain performance standards during the review process.

[98] See for instance Grabowski (1976), Grabowski and Vernon (1983), and Peltzman (1974).
[99] For a summary of the role of AIDS activism see Siplon (2002).
[100] Public Law 102-571, Title I, §103.

Third, the law required the FDA to levy fees on firms that request product approval so that this would generate resources to hire additional reviewers to expedite the process. As the PDUFA included a sunset clause after five years, the user fee had to be reauthorized, which indeed happened in 1997, 2002, and 2007. Other changes that accommodated the requirements of the pharmaceutical industry followed suit, for example the FDA Modernization Act of 1997[101]. The Act added official industry representatives to FDA advisory committees, which turned an at times adversary relationship between the regulator and the regulatee into a collaborative partnership. The Act also enshrined a new philosophy with regards to the protection of public health. Instead of solely keeping unsafe medicines off the market, promoting public health also entailed the timely approval of new drugs. Accordingly, the modified mission statements asks that the FDA

> *"shall promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."* (U.S. House of Representatives 1997, p. 27)

These changes turned out to be successful in bringing more drugs to the market in shorter time. The General Accounting Office (GAO) found that PDUFA funds allowed the FDA to increase the number of new drug reviewers by 77 percent in the first eight years of the Act, while over the same period the median approval time for non-priority new drugs dropped from 27 months to 14 months (U.S. General Accounting Office (GAO) 2002). Moreover, over the period 1987 to 1996, the percentage of products first marketed in the United States

[101] Public Law 105-324.

rose from 20 percent to 43 percent, thereby making the country the worldwide leader in the approval of new medicines (Kaitin and Healy 2000, pp. 12-13). The FDA's competitive position improved to an extent that Japanese and in European policy started considering the agency as a best-practice model according to which the own regulatory practice should be reformed. The shift of the FDA from a regulatory hurdle towards a comparative institutional advantage for drug-developing industries is emblematic for the transformation of neoliberal, competitive nation-states. It also shows that, where regulatory approval involves a government agency, crucial coordination efforts also in a liberal market economy such as the United States is based on informal lines of communication: Unimpressed by the European Commission's announcement to streamline its pharmaceutical approval process in the hope to bring research back to Europe, Dr. Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research, stated that the FDA's competitive status would not be threatened. The real advantage of the FDA, in her view, was its consulting process with the industry and with companies throughout the entire drug development process (Michaels 2001).

In a similar vein, two other important changes lowered the authority of the FDA in favor of the industry whose products it regulates. To begin with, in 1997 the FDA granted pharmaceutical companies the right to advertise their products directly to consumers. This practice has greatly altered the relationship between doctors and their patients. Its effects on public health in the United States became fiercely debated (Findlay 2000). Second, FDA regulations now allow pharmaceutical firms to promote, and doctors to prescribe, medicines for indications other than those they were originally approved for. Once a drug

is cleared by the FDA, it can be described by the doctors in any way he sees fit. In fact, many of today's top-selling drugs deviated from their original career. For example, Pfizer's top-selling antidepressant drug Prozac was initially marketed as an appetite suppressant. Viagra, by the same company, was initially developed as a hair loss remedy. On the other hand, such off-label prescriptions can lead to adverse side effects of the drug[102]. In both cases, the FDA deviates from practices of regulatory agencies in other countries (Ceccoli, p. 152).

These regulatory practices of the FDA have affected positively the institutional comparative advantage that the U.S. healthcare market provides for pharmaceutical companies to carry out their business in a profitable way. Yet they have also become a reason for concerns. For instance, at a hearing for the continuation of PDUFA in 2002, Congressman Sherrod Brown (D-Ohio) criticized the acting FDA Commissioner Lester Crawford for bragging about the agency's performance:

> *"I grew up thinking the FDA was there to protect safety and not to play a role in enhancing the U.S. market share. You are a regulatory body, and you are not a subsidiary of the drug industry…I wonder where is the separation and who is in control? Is the FDA in control or is it the industry that it regulates in control?"* (U.S. House of Representatives 2002)

[102] The intended and unintended side effects of prescribing drugs for various indications as soon as they are approved are discussed by Law (2006).

While the changes of the FDA's regulatory practices will be revisited in the concluding chapter, one ideological paradigm shift should be pointed out already here: Given the FDA's origins and its twofold mandate of law enforcement and consumer protection, traditionally the FDA had concerned itself with preventing drugs from entering the market that should not be approved. But drug safety is an inherently relative concept. The risk of a particular medicine always has to be gauged against the benefits. As we have seen, a combination of pharmaceutical interest representatives and AIDS activists urged the FDA to make new drugs available to the public sooner and to expedite the drug review process. Reacting to these concerns, the FDA struck a different balance between risks and benefits that expands the definition of public health promotion. Read this way, the FDA acknowledged that public health is also in peril when consumers do *not* have access to new and effective therapies. Yet this understanding focuses on the technology supply side alone: It equals market approval with access and ignores whether the price of a new drug may be the decisive bottleneck towards new and effective therapies. As the 1962 Kefauver amendment demonstrated, it has not been politically feasible to extend the FDA's mandate to include such concerns. The next chapter will analyze how the absence of price caps for prescription drugs was also kept out of other federal organs and agencies.

5.9 Conclusions

This chapter took a historic view on key aspects of the institutional support structure that profit the biotechnology in the United States. It demonstrated that despite the dynamism of the industry, the creative destruction, and the rhetoric of market competition, historically various types of government interventions created the organizational and institutional

foundation for the sciences to come. Time and again, the politics of economic stimulus trumped the rhetoric of free markets (claim 2).

The industry came into being at a critical historical juncture when scientific advancements coincided with neoliberal economic concepts to promote the supply-side. Throughout the 1970s the ascent of biological sciences and neoliberal ideologies were not limited to the United States. But by the 1980s, the institutional support structure already in place received a boost from resource mobilization for the supply-side of these new technologies. This created an institutional comparative advantage for the biotechnology industry to rise first and most vigorously in the United States. As expected from a liberal market economy, the rule of law, especially sophisticated intellectual property protection, as well as elaborate capital markets are key components to a favorable institutional support structure for a fast-past innovative industry such as biotechnology. Here, the role of the state is more of an arbiter that has to readjust regulatory efforts. Yet other ingredients, specifically the scientific infrastructure, came about only as a result of substantial federal support efforts, often times in conjunction with military build-up.

Historically, the different waves of defense spending helped solidify clusters of scientific excellence that arose among a fragmented landscape of institutions of higher education. Wealthy entrepreneurs and their philanthropic outlets, especially the Rockefeller Foundation, aimed at ‘making the peaks higher’. They funded research universities to overcome America’s scientific and technological deficit vis-à-vis European nations and – as in the case of molecular biology – at times introduced new research paradigms. Yet

World War II and the massive efforts to build an atomic bomb showed the need for concerted federal intervention in science and technology. Clustering and ‘making the peaks higher’ were important organizational decisions that favored not only research universities but also a few of the land grant universities, in particular MIT, initially established to disseminate agricultural and mechanical knowledge.

After World War II, the reconversion of these military resources for civilian purposes ushered in a division of labor, in which publicly funded basic research would be made available to for-profit actors who carried out applied research for commercialization. This setup also profited the development of biomedical sciences. Most important was the evolution of the NIH into the world’s largest organization for medical research. NIH not only increased the resources for biomedical research, it also institutionalized funding mechanisms based on peer review, which continued to allocate more resources to already existing clusters of excellence.

Eventually publicly funded research became increasingly scrutinized to deliver commercial value at a time when the United States was challenged to keep its leadership in international competition. Starting in the late 1970s, the neoliberal understanding gained traction that the increase in global competition required the state to promote domestically the advancements of new technologies. In the 1980s various policies to strengthen the supply-side of such technologies were devised. For instance, profit incentives for researchers were introduced by allowing them to patent federally funded research, and to transfer technologies to the private sector. These measures were successfully taken up by

biomedical researchers and business actors in a number of locations in the United States. As the interviews in the previous chapter confirmed, the competitive first-mover advantage could keep its momentum and is still present due to the clustering of the biotechnology industry in a number of regions in the United States.

Moreover, independent from the location within the United States, there were important policy measures that promoted the competitive advantage of the country's fledgling biotechnology industry as a whole. A regulatory environment conducive to speculative, risk-taking entrepreneurial activity helped with the provision of venture capital as well as with stock markets that allowed the VC industry and other investors to recoup their stakes in this new industry. Equally important for the comparative advantage of the institutional support structure for biotechnology in the United States is the question of patenting. Starting with the U.S. Constitution, the protection of intellectual property meandered between favoring at times inventing and at times copying. At the end of the 19th century, a political movement against the increasing influence of powerful corporate actors led to the adoption of anti-trust legislation. By contrast, at the end of the 20th century, the neoliberal view of promoting individual entrepreneurial activity prevailed.

Specifically for the newly arising biotechnologies, pivotal decisions were taken by Congressional legislative efforts, but became de-politicized in the court system. Once relegated to courts, key biotechnology-related decisions have not taken up principled concerns but have rather come down on the side of what is pragmatic and promotional from a business viewpoint. Equally in line with the needs of the industry turned out to be a

regulatory framework, which assesses the risks of biotechnologies on the product and not, as in Europe, on the process.

While this put the United States into a comparative institutional advantage with regards to the commercialization of genetically modified crops, the pivotal gatekeeper for launching biomedical products in the U.S. market is the FDA. Here the starvation of federal bureaucracies prescribed by the Reagan administration had an ironic, unintended consequence. Overwhelmed and underfunded, the FDA became less conducive to the needs of the pharmaceutical manufacturers. Pressured also by social actors such as the AIDS rights movement, the FDA broadened its mandate for the promotion of public health by approving new treatments and drugs faster. It took until the early 1990s before the agency successfully streamlined the drug approval process in favor of the needs of the industry it was supposed to regulate. Here we see how the neoliberal state has shifted its functions: The institution is transformed from being conceived as a regulatory hurdle into a support structure. Streamlined regulatory provisions are conceived as international competitive advantage for businesses in search for ‘regulatory arbitrage’. Hence, the transformation of this key regulatory institution is not so much an example for free-market rhetoric, but rather for politics to promote economic activity.

As the FDA changed its approval philosophy to make access to drugs easier, the question of whether this may not also be a matter of their pricing was deliberately kept out of the FDA’s mandate. Since also the NIH made it a point not to interfere with market mechanisms for drug pricing, this leads over to the next claim: The absence of federal price

controls provides a comparative advantage for the biotechnology industry in the United States (claim 3). The next chapter will therefore analyze how the United States privatized healthcare system came about and what the effects are for the pricing of prescription drugs in this country.

Chapter 6: Healthcare in the United States: Of Price-Setters and Price-Takers

6.1. Introduction

The previous chapter outlined how institutions of the American political economy contributed to a comparative institutional advantage for the generation and commercialization of biotechnologies in the United States. Yet any analysis merely from the supply side would still be bound to and confirm a neoliberal perspective on the political economy of the biotechnology industry. Therefore, this chapter will address the institutional setup of the demand side for biotechnologies. In theory, demand for these technologies can be defined in many different ways. In practice, however, as confirmed by the interviews in chapter 4, it is the demand from the American healthcare system that is crucial. This chapter will therefore ask how and why the United States healthcare system provides such an exceptional incentive structure for the biotechnology industry. The answer will confirm claim 3: As the biotechnology industry matured and became fully embedded in the blockbuster drug business logic of pharmaceutical companies, the unparalleled incentive structure and the revenues provide for by the fragmented United States healthcare system became increasingly important. The absence of federal price controls for prescription drugs has become a crucial comparative advantage for the biotechnology industry in the United States.

The absence of federal drug pricing oversight is one of the many consequences of the evolution of the American healthcare system. Historically, the provision of health services has always been dominated by private entities, whereas public programs have repeatedly

been relegated to the second tier. Most of these developments predate the rise of the biotechnology industry. Yet a brief recapitulation of this history is important to understand why over time a complicated mix of private and public activities has developed into a labyrinth of conflicting incentives. The historical background is also necessary to understand why this institutional setup turned increasingly hard to reform. For their part, the pharmaceutical and biotechnology industry have a vested interest in not reforming the current system, because it leaves the pricing of prescription drugs largely unregulated.

To prove my third contention that America's healthcare system is a key component of the country's comparative advantage for fostering the biotechnology industry, this his chapter is organized as follows: Section 6.1.1 will address some of the basic dilemmas that occur when providing health as a marketable good. There is a conflict between deciding on what treatment is necessary and at what cost**.** The institutional setup to mediate this conflict lies at heart of any nation's healthcare system. Unlike any other wealthy industrialized country, in the United States political decisions have regularly preferred market-based solutions. Section 6.2 will therefore put the outcome of these market-led health policies in an international perspective. Key data for health statics will be presented to illustrate that in international comparison with other wealthy, industrialized nations, the United States relies more than any other country on private health insurance, while at the same time having the highest expenditures on healthcare, including drugs.

Yet the fact that the United States does not have a universal healthcare system is not only remarkable in international comparison. The historic overview in Section 6.3 explains how

America's market-based healthcare system was established in contrast to Social Security, the country's public, universal provision of a pension. The political momentum that allowed President Roosevelt's New Deal administration to establish Social Security was not sufficient to bring about a universal healthcare system at the same time. After this failure, private health insurance emerged as a wholesale alternative to public health insurance after World War II (6.3.1). An institutional division of labor emerged which saw the private sector in the lead and the public programs picking up the slack. A case in point was the passage of Medicare and Medicaid in 1965 (6.3.2).

Important for the arguments this study investigates, section 6.4 explains how, once this system was in place, healthcare reform has become an increasingly difficult endeavor. With private health actors becoming the price-setter, political interventions to curb cost hikes became increasingly necessary, but had mixed results (6.4.1). Ample room will then be given to the failed initiative of President Clinton for healthcare reform in 1993/4 (6.4.2). On the one hand, this episode illustrates how the American healthcare system, despite broadly acknowledged shortcomings with regards to coverage of the population and the increasing costs, has turned into a labyrinth of insurmountable and contradictory vested interests. On the other hand, the rejection of the Clinton reform proposal became a rallying point for the biotechnology industry, which for the first time organized its interests in a coherent and institutionalized manner. In the aftermath of President Clinton's failure and with no chances for comprehensive healthcare overhaul, the issue of prescription drug prices became a central point of contention. Here the generally fragmented and constricted role of the federal government in health provision translated into limited government

leverage to curb prices for prescription medicines (6.4.3). As these costs continued to rise, the extension of prescription drug benefits to one of the most needy parts of society – Medicare recipients – became a political issue. The next section (6.4.4) therefore explains how the Medicare Modernization Act (MMA) of 2003 deliberately abstained from establishing the federal government as the largest purchaser – and price-setter – of prescription drugs. The market-based solution that Congress adopted instead is another example for why *laissez-faire* solutions are *never* inevitable or natural outcomes, but *always* politically fabricated. By giving preference to a private solution instead of an overarching public effort, American politicians once again paid tribute to neoliberal ideology.

The MMA was formulated in line with the interests of biotechnology and pharmaceutical industries, which demonstrated their political clout during the legislative reform efforts. Section 6.5 therefore takes a look at the machinery that biotechnology and pharmaceutical industry established to represent their interests vis-à-vis political decision makers in Washington. Relevant for the arguments put forward in this study is not interest group lobbying *per se,* but rather *on which issues.* The lobbying efforts and the political wrangling of biotechnology and pharmaceutical industries to shape the MMA in their favor therefore reveal how relevant America's fragmented healthcare market without any federally invoked price cap has become for these businesses. Moreover, their interest group representation is also a factor to be reckoned with in subsequent U.S. healthcare reform debates that started under the new administration of President Obama in 2009. Section 6.6 will summarize the exceptionalism of the American healthcare system in its present form

and the comparative institutional advantage that it presents for the biotechnology industry. Exceptionally high prescription drug prices have led to a call for a bigger role for government. The prospect of these and other challenges to the blockbuster drug regime that could become consequential also for the biotechnology industry are ultimately addressed in the final chapter 7.

6.1.1 The Dilemmas of Healthcare Markets

In theory, markets bring together a vast number of sellers that compete with each other to sell homogenous commodities to a vast number of buyers, who can make rational, well-informed choices about their purchase, for which they pay the full price. Although very few real markets live up to this standard in actuality, health economists have repeatedly stressed the particular insufficiencies that healthcare markets are fraught with (Donaldson and Gerard 2005; Zweifel and Breyer 1997). To begin with, if confronted with a debilitating disease or death, the notion of rationality looses its utility. People are making sacrifices and pay whatever they can to obtain the health goods and services they consider necessary. In the language of economists, prices for these goods and services are inelastic of demand. And since the costs of medical services are high and the need for them is uncertain and unevenly distributed, it makes sense for a risk-averse individual to obtain insurance. Yet such insurance adds another layer of complexity to the imperfect, asymmetrically distributed, information that is the general dilemma of the healthcare market: Doctors know more than patients do about treatment options. Patients in turn know more about their need for care than insurers do. This creates three central dilemmas to finance medical care: agency, moral hazard, and adverse selection (Hacker 2002, p. 181). The agency dilemma occurs because the patient has to yield decision power to the doctor over the treatment,

without having proper information about the quality. For the insurers, by contrast, the agency dilemma stems from the fact that the party that receives the payment - the doctor - is the same that discovers the problem, decides which services the patient needs, and also sets the price for the treatment. How could the insurance company be confident that a service was not delivered because the doctor knew that the patient had an insurance policy (Madison 2005, p. 47)? From the viewpoint of an insurer, this leads to the dilemma of 'moral hazard'. Once insured, the individual has fewer incentives to prevent risk-taking behavior, and also has considerable less interest in constraining the price for a treatment. The third dilemma, adverse selection, results from asymmetrical information between an individual and the provider of health insurance. The insurance provider has an interest to offer coverage only to healthy individuals, whereas these individuals may opt out of health insurance to save the money. With healthy individuals opting out, the premiums for the insured have to be higher, thereby precluding low-income and high-risk people from coverage. Therefore, adverse selection makes it impossible that private action of individuals and insurers leads to the public good of broad-based health insurance coverage.

Over time, all advanced industrialized nations have been confronted with these moral dilemmas. At the heart of the medical politics problem is the question, who should reasonably best mediate the abovementioned agency problem while controlling costs? Should it be the market, the medical profession, or the state? Driven by politics, economic concerns, and efficiency considerations, different answers have been given in different countries. As the next section will explore, the politics of healthcare in the United States is

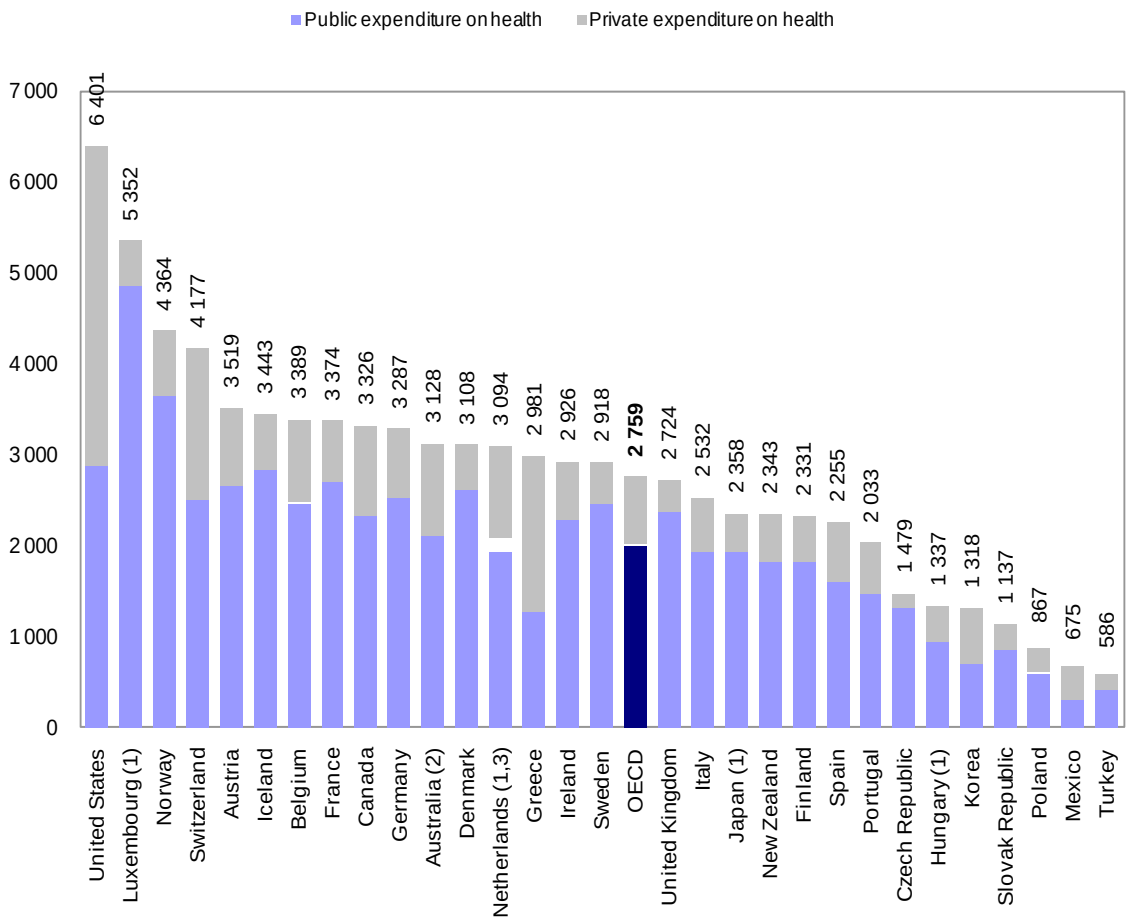
most distinct in its vast reliance on private market services, as well as with regards to the overall level of prices.

6.2 The U.S. Healthcare in International Comparison

American exceptionalism in healthcare rests on four pillars: First, the United States spends more than any other country on health. In 2005, when the other wealthy industrialized nations of the Organization for Economic Cooperation and Development (OECD) allocated, on average, 9 percent of their GDP to health, the United States spent 15.3 percent (OECD 2007, p. 89). Also per capita, the United States outspends any other industrialized nation by far. In 2005, the country devoted $ 6,401 per capita to health (see Figure 6.1 below). Remarkably, this amount was not only 20 percent higher than the health expenditures of the next country, Luxemburg, but it equated to more than two and a quarter times the average of OECD countries ($ 2,579).

Figure 6.1 Health Expenditure Per Capita, Public and Private, 2005

(Purchasing Power Parity $)



1: 1995-2004; 2: 1997-2005; 3: 1998-2005.

Source: (OECD 2007, p. 87)

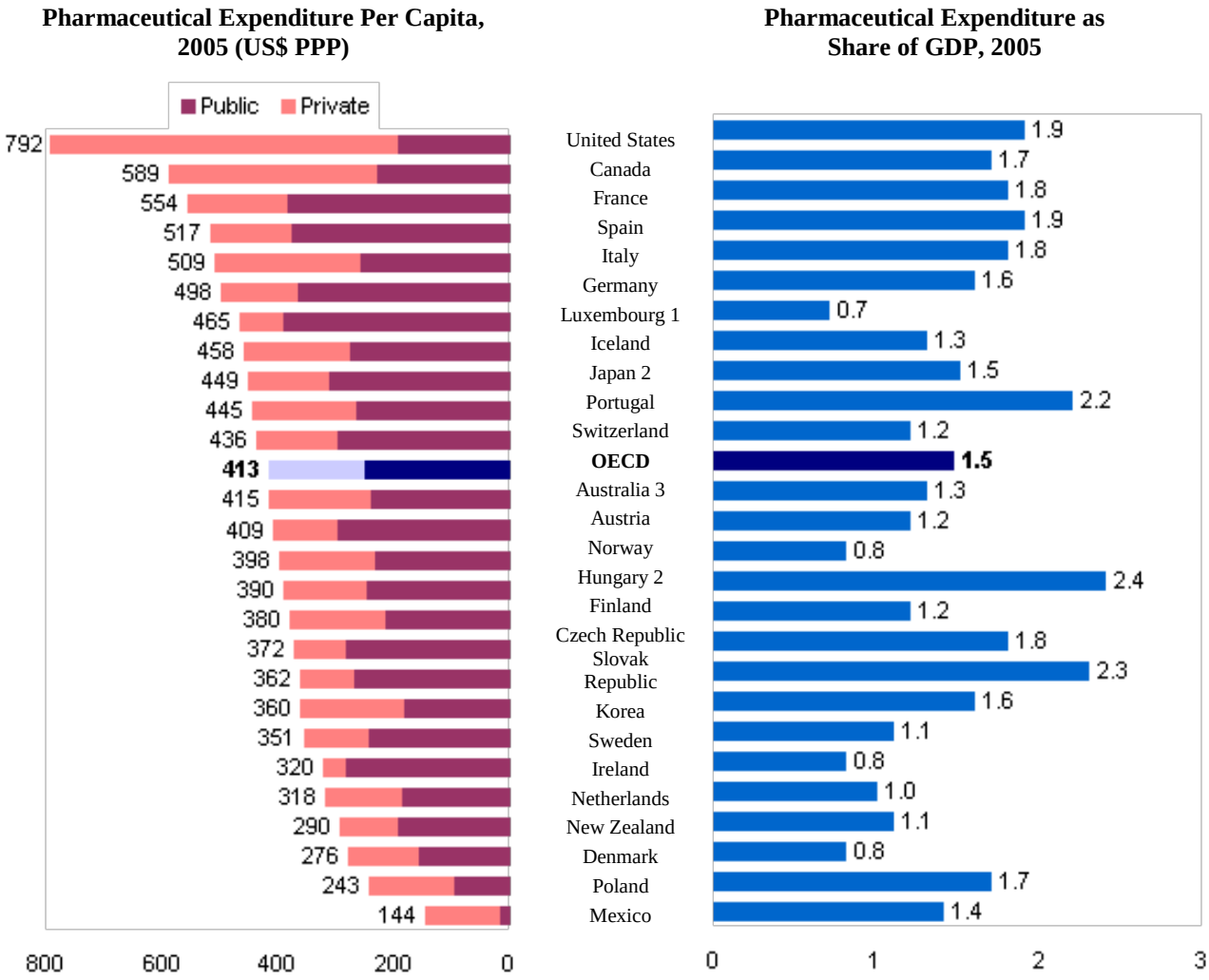
Second, the share of private health spending – by individuals and private insurance providers – is higher than anywhere else. Unlike all other OECD countries, in which public health expenditures account for the major share, the United States is the only country in which a majority of health expenditures are private (55 percent, see Figure 6.1 above).

Third**,** the United States is the only advanced industrialized nation that does not have a publicly guaranteed universal or near-universal level of healthcare coverage. In the United States currently only about 27 percent of the population – the elderly, poor and disabled – are covered by publicly financed health care. Another 59 percent are covered by private health insurance, leaving 14 percent of the population – some 48 million- without any coverage at all (OECD, 2007, p. 97).

Fourth, and most relevant for surveying the biotechnology industry, the United States has the highest expenditures for pharmaceuticals. In 2006, the global market was worth $608 billion, of which the United States alone accounted for $274 billion, about 45 percent (OECD 2008, p. 58). And although pharmaceuticals represent a smaller budget of the U.S. healthcare expenditures than the average of OECD countries (13 versus 17 percent), the United States nevertheless outspends the rest of the OECD by far on drugs: Compared with the average of all OECD countries, which in 2005 directed 1.5 percent of their GDP to pharmaceuticals, the United States spent almost a quarter more (1.9 percent). Americans also account for the highest annual per-capita-spending on drugs - $ 792 - which was 86 percent above the OECD average (see Figure 6.2). Moreover, the United States was also unique in that less than a quarter (24 percent) of pharmaceutical costs were public expenditures, whereas more than three quarter were private (OECD 2007, p. 93). Last but not least, costs in the United States for pharmaceuticals have risen disproportionately faster than elsewhere. Since 1995, throughout the OECD, expenditures for drugs have risen by an average of 4.6 percent annually, which is higher than the annual 4 percent increase in total health spending over the same period. Yet the United States is the only country where

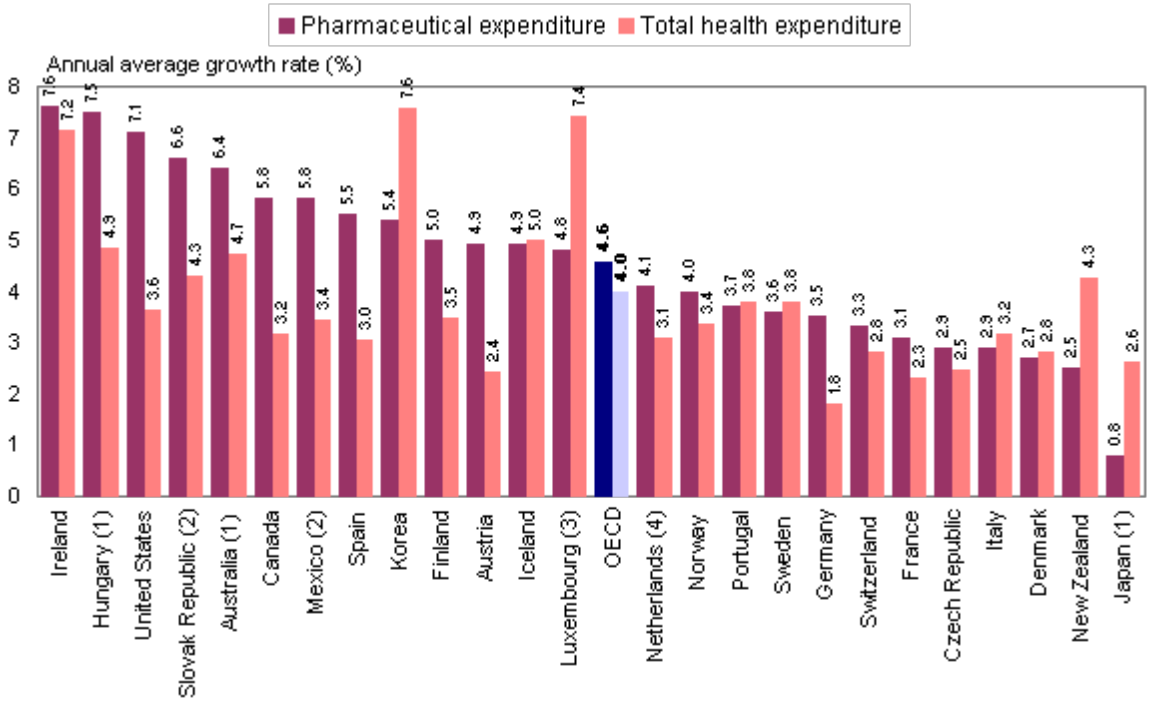
pharmaceutical expenditures have grown almost twice as fast as general health expenditures (7.1 versus 3.6 percent, ibid.).

Figure 6.2: Comparison OECD Pharmaceutical Expenditures, 2005



1. Prescribed medicines only. 2. 2004 3. 2004-05

Figure 6.3: Real Annual Growth in Pharmaceutical Spending and Total Health Expenditure Per Capita, 1995-2005



1. 1995-2004. 2. 1999-2005. 3. 1995-2003. 4. 1995-2002.

Source: OECD Health Data 2007.

In many regards the United States' high expenditures on healthcare do not translate in longer or healthier lives: Whereas in 2005 the OECD average life expectation at birth was 78.6 years, it was 77.8 years in the United States (OECD 2007, p. 21). In terms of infant mortality, America's rate of 6.8 per thousand is the fourth highest among OECD countries. In part, this lower performance is a result of the United States' discrepancy in health provisions between those who have access to health insurance and who do not[103]. A comparative analysis between the United Kingdom, which has a national health care

[103] Moreover, these discrepancies are overshadowed by other inequalities such as gender, age, and ethnicity (Patel and Rushefsky 2008).

system that covers every individual, and the United States, points into a similar direction. The study found that Americans, at all points of the socio-economic spectrum, are significantly less healthy than their English counterparts (Banks et al. 2006).

In conclusion, these data corroborate the findings from the interviews in chapter 4: Its profitability and fragmentation turns the United States healthcare market into a comparative institutional advantage for biotechnology actors. The system that provides Americans with healthcare, including drugs, is generally less comprehensive in terms of coverage of the entire population, and relies less than any other on public healthcare. And although it is more expensive, it is not necessarily better than the system in comparable affluent industrialized nations. Taken together, these features of the American healthcare market have created an exceptional incentive structure for pharmaceutical companies and for medical biotechnology. To understand why this is the case, as well as whether there are prospects for change, I will next look at the history of the United States health insurance system.

6.3 History of US Healthcare: The Dominance of Private Healthcare

6.3.1 Early Legislation and Reform Efforts

Obviously the provision of healthcare services in the United States predates the biotechnology industry. This brief historical overview illustrates how a privatized, market-led health system became established and entrenched. Time and again, political decision relegated the public sector to the second tier: Instead of directly providing health-related services, an institutional framework for healthcare was created in which public authorities

deliberately stepped back and handed over tasks to private actors. As a consequence, these actors turned out to be the price-setters, whereas the public became the price-taker. Time and again, political interests became more entrenched, and the hurdles to abandon this path continued to rise. This political dynamic continues to date, when a maturing biotechnology industry has turned into an organized political actor with a vested interest to upkeep the institutionalized status quo.

Whereas historically a sick person would pay a doctor a fee for his services, the first, privately organized, collective financing of medical care in the United States was conceived during the Great Depression. Employers increasingly began offering health insurance to their employees as an attempt to calm down a radicalized workforce and to prevent unionization. Particularly consequential turned out to be a Texan hospital prepayment plan, later labeled 'Blue Cross'. Thanks to its special charter and tax exempt status in state after state, Blue Cross quickly grew into a nationwide system of voluntary insurance that was self-consciously and successfully presented as the private alternative to governmental involvement in healthcare[104].

A decisive watershed for the future of national health turned out to be the elimination of healthcare from the Social Security Act of 1935[105]. This legislation initially included

[104] Blue Cross Publications of that time herald the Founding of Blue Cross as a linkage of patriotism and voluntarism: *"The Blue Cross Plans are a distinctly American institution, a unique combination of individual initiative and social responsibility. They perform a public service without public compulsion."* And: *"Private enterprise in voluntarily providing hospital care within the reach of everyone is solving the public health problem in the real democratic way. The continued growth of the Blue Cross Movement might well be considered the best insurance against the need of governmental provision for such protection."* (quoted in Rothman (1997, p. 31)).

[105] Public Law 74-271 .

compulsory, state-by-state program for health insurance, which was fiercely opposed by the medical profession organized by the American Medical Association (AMA). Against these opposing forces Roosevelt decided to drop health insurance from the bill and invest his political capital on the passage of the other elements of the Social Security Act to alleviate the burdens of poverty, unemployment, and old age. As a consequence, Social Security and a pension system for all Americans over age 65 developed into the most valued federal program. Conversely, the decision against a similarly encompassing health insurance bill set America's healthcare on a path that has been hard to change until this day[106]**.** Four issues stand out:

To begin with, health insurance became established as a service that was based on employment. Promoted by medical providers, employers and insurers, companies increasingly enrolled their employees in private group hospital and physician plans. This trend was backed in 1939 by a ruling of the Internal Revenue Service that allowed the deduction of fringe benefits from the employer's taxable income. This decision became crucial as during World War II, labor became scarce. Because the National War Labor Board prohibited wage increases, employers competed for workers with fringe benefits such as healthcare. By the end of World War II, the number of Americans enrolled in work-related healthcare had tripled and, by 1950, more than half of all Americans were covered by private health insurance, which became the core healthcare provision in this country (Hacker, p. 232).

[106] Proposals for a universal healthcare continued to fail repeatedly at a time where Social Security became rooted and expanded. These intertwined but ultimately divergent paths led to a setting in which private pensions were built on the top of Social Security, whereas private health insurance emerged as a wholesale

Secondly, after World War II the political struggle about health insurance became embroiled in the climate and rhetoric of the Cold War. President Truman's repeated efforts to introduce national healthcare were defeated by a coalition of companies, insurers, and the medical profession. Together with conservative politicians these allies mobilized anti-communist fears and labeled Truman's national health program as 'socialized medicine'[107], a catchword that has survived until today.

Thirdly, after the defeat of Truman's health initiatives, and in light of the anti-union Taft-Hartley Bill passed in 1947, organized labor increasingly focused on negotiating health plans for their members. These plans became an important organizing tool for unions to safeguard their members' loyalty. While collective bargaining agreements between employers and organized labor led to relatively comprehensive private health insurance within a firm or an industry, these arrangements undermined the larger goal of healthcare protection for a broader constituency (Hacker, pp. 231-2). Not only did unions' interest in a national healthcare solution decrease, but it was even feared that such a solution may compromise the achievements of the unions for their members - another argument that reverberates in contemporary health reform discussions.

Lastly, while a growing number of the population became covered by private health insurance, the market leader Blue Cross was increasingly attacked by other private,

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alternative to public health insurance. The argument of the "Divided Welfare State" was eloquently made by Jacob Hacker (2002) on whose work this section is based.

[107] In the words of the AMA: *"If we can get ten million more people insured in the next year and ten million more in the next year, the threat of socialized medicine in this country will be over"*(Campion 1984, p. 162).

commercial insurers. Unlike Blue Cross, which charged everyone in the same community the same rate, the private contenders divided the population into subgroups based on risk and charged different rates. Blue Cross had to follow suit, and as a consequence, the risk pool became more and more fragmented and stratified. Throughout the 1950s, as employers and organized labor increasingly subscribed to health plans based on different fees for different risk levels, affordable health insurance became problematic for those left behind in a community risk pool that held a greater proportion of poor and marginally employed, of chronically sick and disabled people, and of the elderly (Madison 2005, p. 61).

Such developments notwithstanding, President Eisenhower preferred not to meddle with the public-private mix that already existed. His most consequential initiative was the creation of the Federal Employees Health Benefits Program (FEHBP) in 1959. Rather than have the government assume the health risk and related costs for its employees, under FEHBP the government contracted out healthcare to private plans and only oversaw the enrolment, and the payment of a fixed amount towards the premiums that these private providers charged. At its time, the FEHBP was the largest voluntary employee group health insurance program in the world. Equally important, however, by outsourcing federal tasks to the private industry, a precedent for numerous healthcare reform proposals was set that reverberates until this day: Alternatives modeled after FEHBP were presented throughout the discussions about Medicare in the 1960s; FEHB was rediscovered and served as a template for the Clinton administration's failing Health Security Plan in 1993; FEHBP also became the blueprint for the overhaul of Medicare in the 2003 Medicare Reform Act (see

6.4.4 below), which extended the role of private health plans towards the management of prescription drugs (Hacker, p. 242). And also in the political struggle to reform healthcare under the administration of President Obama extending the coverage through private health insurance was offered as an alternative to the so-called 'public option' (see 7.8 below).

6.3.2 The Passage of Medicare and Medicaid

As employment-based health insurance became the core provision for healthcare, the gap between those covered and those left out widened. It became obvious that those who were not covered by a work-based health plan or too poor to afford alternative insurance, as well as those too old, disabled, or chronically ill, would not be served by the voluntary health insurance system. The need to cater to those left out gained momentum and a window of opportunity for major reform opened after Lyndon B. Johnson's landslide victory in the 1964 election. Unlike Roosevelt in 1935, Johnson decided to spend his political capital on passing national healthcare legislation. As a result, Medicare and Medicaid, national healthcare programs for the elderly and the poor, were adopted as part of the Social Security Act of 1965[108]. At the same time, however, these programs not only reflected the restricted options for healthcare reform back then, but they also perpetuated the impediments for extensive healthcare overhaul until today.

Medicare was a federal hospital insurance program and a physicians' insurance plan for all citizens over 65 at little expenses to themselves. Medicare was conceived as a self-sustaining program financed by general income tax revenues in line with those for Social

[108] Public Law 89-97.

Security. That connection was intentional, not only for administrative purposes, but also to profit from Social Security's popular reputation as an 'earned right' to which workers were entitled due to the contributions they had made during their working years (Rothman, 1997, p. 84). In theory, Medicare stipulated to pay physicians for their services based on the vague proposition that charges had to be 'customary and reasonable'. In practice, the unintended consequence of this legislation was an in-built cost-hike and physicians' incomes increased immensely after the adoption of Medicare. Moreover, Medicare was exclusionary in terms of what was covered and who was eligible. For example, it did not provide assistance with prescription medications. This caveat turned out to be consequential for contemporary senior citizens who have been affected by the steep increase in prescription drug prices. At the time of its adoption in 1965, however, this was less of a problem as prices for prescription drugs were still low. The bigger challenge then was to extend coverage towards other parts of society that private health insurers had no interest in, such as the unemployed, the chronically ill, or children.

Partly rectifying such shortcomings, partly as an afterthought to the Medicare legislation, the Social Security Act of 1965 also passed Medicaid. Medicaid for the first time provided publicly financed health coverage for low-income families with children and low-income aged (some of which also obtain Medicare) or disabled individuals. Financed jointly by the federal and by state governments, most responsibility for defining eligibility and service provision criteria, and for administering the program, was devolved to the states. Although adopted in 1965, Medicaid was not available in every state until 1982. Today, Medicaid covers 59 million low-income Americans, including one quarter of all U.S. children.

Medicaid is financed by public means, but its services are mostly provided by private entities, predominantly Health Maintenance Organizations (HMOs) which are remunerated for their services. In 2006, the overall financial outlays of Medicaid services were $304 billion. Two groups with special care needs, the elderly, many of them in nursing homes, and the disabled make for 70 percent of Medicaid's expenditures, while accounting only for a quarter of all Medicare beneficiaries. Provision of prescription drugs through Medicaid is not mandatory and outlays for medicines account for less than 6 percent[109]. However, all states have some mechanisms for at least partial coverage of prescription drugs and further below (see 6.4.3) I will explain how they have turned into passive price-takers of what the private sector dictates.

In sum, these first governmental programs did not prove to be a stepping stone towards national health insurance, but rather a dead end alley for the extension of benefits. By providing some healthcare coverage for the elderly, the disabled and the poor, these programs relieved the private insurers from the potential financial burden that coverage of the most vulnerable segments of the population would have implied, thereby re-manifesting the centrality of the private insurance system. While Medicaid outsourced the provision of services to private actors, Medicare created an incentive structure that paved the way for increasing healthcare costs for the public at large. Hacker therefore concludes that

[109] All data see Kaiser Family Foundation (2009).

> *"[t]he federal government had first built up the technological prowess of the medical complex, then become a generous subsidizer of private health insurance, and then finally stepped in as a largely passive financier of private medical care itself."* (p. 247)

This institutional setup does not benefit all members of American society equally, but it turned out to be advantageous for the pharmaceutical industry and, in its tailwind, biotechnology.

6.4 Challenges to Reform Healthcare

6.4.1 Cutting Costs

With another opportunity for comprehensive health insurance extension foregone, throughout the 1970s the debate about healthcare was dominated by increasing healthcare costs. Federal health outlays quadrupled from 0.4 percent of GDP in 1965 to 1.6 percent in 1974 (Office of Management and Budget (OMB) 2009, Table 16.1.)[110]. This time, the political odds were stacked against the medical profession. Doctors had initially profited from the defeat of national health insurance and the alternative based on businesses enrolling their employees in private health insurance plans. Yet this private set-up put the medical profession at odds with other private actors, such as corporations and private insurers. Unlike in other industrialized countries where health care costs were supervised by a federal institution or policy, in the United States cost control was left over to market forces. Exacerbated by an economic crisis in the 1970s, companies became increasingly conscious of their expenditures for their employees' health insurance.

[110] This figure rose to 5.2 percent in 2007.

The response of cost-conscious insurance leaders was the establishment of managed care vehicles, such as HMOs. These prepaid group plans integrate the finance and the delivery of medical care. For patients, only visits to professionals within the HMO network are covered by the policy. The HMO also clears prescriptions and other care needs before they are covered and an in-network primary physician handles referrals. Doctors, organized into panels, either received a salary or a fixed fee per patient treated. In both cases HMOs should generate cost cuts by incentivizing doctors for treating less, and not, as under the previously prevalent fee-for-service model, for treating more.

In the mid-1980s, 95 percent of all employees enjoying work-related health insurance were covered by a fee-for-service agreement. By 2000, HMOs and managed care had come to dominate the field and 92 percent of employment-sponsored health insurance is conveyed by a managed care plan. Moreover, more than 36 states provide Medicare services through managed care. Yet as it turned out, managed care did not achieve the cost savings that its proponents had promised: By the early 2000s, health care costs were on the rise again, increasing more than three times the rate of general inflation, indicating the short-lived nature of the restraints that managed care wielded over cost hikes. Likewise, the style of care management turned out to be unsustainable. Rising complaints by patients and doctors led to a backlash against managed care so that many restrictions on health care utilization, such as gatekeeping requirements, and the restricted access to physicians and hospitals, were revoked (Oberlander et al. 2005, p. 18). Full-scale HMOs became complemented by

other rationalized care schemes, such as Preferred Provider Organization (PPO) and Exclusive Provider Organization (EPO) plans[111].

6.4.2 The Clinton Healthcare Reform Failure

Managed care as a tool for cutting costs also stood central in President Clinton's proposal for health insurance overhaul, the Health Security Act of 1993, in which the federal government was considered to be the ultimate arbiter in a so-called 'managed competition'. Clinton's proposal of 'competition within a budget' wanted to achieve universal health insurance through competing private plans. Americans would purchase insurance through regional purchasing cooperatives set up by states, which would also monitor the competition among them (Hacker 1997, p. 4). This complex proposal also included an employer mandate to pay 80 percent of their employees' premium, the elimination of Medicaid, government subsidies for small companies and unemployed, and a cap on insurance premiums as well as the total budget. While explicitly rejecting a Canadian single-payer system of national health insurance, states could establish their own single-payer system if desired (Rushefsky and Patel 1998, p. 67). During the Congressional deliberations of the Act, several alternative reform plans were presented: some were modifications of the Clinton approach, others were single-payer plans, while others relied on more voluntary mechanisms, such as tax breaks. Clinton's plan was unable to muster the political momentum to be passed before the elections in 1994 and failed.

[111] PPOs encourage patients to choose doctors, hospitals, and other providers that participate in the plan by increasing the patients' co-pay if they use 'out-of-network' providers. By contrast, EPOs are similar to an HMO in that a patient has to select a primary care physician who will be responsible for meeting health care needs. In most EPO plans, as with an HMO, 'out-of-network' services will not be covered at all.

As a consequence of the Clinton administration's failure to overhaul health care, throughout the next decade only incremental changes were being implemented. In 1996 Congress adopted the Health Insurance Portability and Accountability Act (HIPPA), which limited the periods during which patients with preexisting conditions could be withheld coverage. The Act also made it easier for employees losing group coverage to purchase individual health insurance. And in 1997, Congress enacted the State Children Health Insurance Program (SCHIP), to aid children in low- and moderate-income families who did not qualify for Medicaid (Oberlander et al. 2005, pp. 11-12).

On a general level, the logjam of reforming healthcare in the United States is exemplary for one of neoliberalism's central shortcomings: the provision of a public good such as health by private actors. On a specific level, there are different reasons for the Clinton Health Security Act's spectacular failure[112]. Some authors concluded that American political institutions are structurally biased against such kind of comprehensive health reform (Steinmo and Watts 1995). By contrast, Jacobs (1995) highlight that comprehensive health care reform failed because of the established patterns of health policy that empowered stakeholders of the status quo: Those with insurance, the medical profession, and the providers of advanced technologies. At the same time, inertia turned out to be preferred over changes, even by those who were considered to be the winners. For instance, HMOs were considered to be profiting from Clinton's drive for cost cutting and efficiency improvement.

[112] Comprehensive analyses about the failure can be found in Hacker (1997), Rushefsky and Patel (1998), and Skocpol (1997).

But HMOs opposed the proposal as they feared governmental regulation and the requirements to insure poor people. Likewise, large businesses stood to gain from the Clinton initiative as they tried to control cost escalation. At the end of the day, however, their main lobbying organ, the Business Roundtable opposed the plan, due to a default resistance against governmental social intervention and the pressure from businesses such as the pharmaceutical industry with a vested interest in the status quo (Jacobs 1995, p. 149). In sum, the failure of the Clinton reform initiative demonstrated that although the financing structure for healthcare was disliked by most stakeholders, the medical system in place had created such a labyrinth of conflicting interests that the basis to find common interests and common goals for change remained diminished.

Two factions eager to keep the status quo were the pharmaceutical industry and, for the first time with an own voice, the biotechnology industry[113]. The two industry's resistance against Clinton's healthcare reform was based especially on two suggested provisions in the reform bill: First, to establish a National Health Board that could investigate 'unreasonable' introductory drug prices. And second, to grant Medicare the prerogative to obtain from pharmaceutical companies a 15 percent rebate on drug companies' average nationwide drug prices (Fox 1993). Even if implemented, these provisions had not granted the government an actual provision to control drug prices. Nevertheless, industry representatives and investors argued that also a 'de facto price setting' would undermine

[113] Further below I will address in detail the formation of the Biotechnology Industry Organization (BIO) (see 6.5).

the industry's financial security[114] as it would curtail the resources available for research. Pharmaceutical and biotechnology companies joined a common line of defense, arguing that their products only accounted for seven percent of healthcare expenditures[115]. Yet they were also aware that these expenses, given the healthcare system as it was, were often paid for directly out of patients' pockets. Consequently, their industries were prone to criticism, particularly from the elderly, whose need for prescription drugs remained uncovered by Medicare. Industry representatives therefore urged their trade organizations to develop jointly a

> "*politically salable Medicare outpatient prescription-drug program"* (Spalding 1993).

As the section below (6.4.4) illustrates, this advice was indeed heeded. Similar to keeping the cake and eating it at the same time, these industries succeeded on extending the coverage (meaning: having new customers) while retaining a maximum of autonomy over prices. But before tackling the reform of Medicare in 2003, it is first necessary to address the relationship between health insurances and costs for prescription drugs. The ways in which the agency and moral hazard dilemma are bridged are a consequence of America's institutional set-up for private service-based healthcare.

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[114] The quote by Fox (1993) of a financial analyst at that time summarizes the line of argumentation that is used until today: *"If you want to kill this industry, put price controls on drugs...They will definitely drive investors into different industries."*

[115] Also during, the healthcare reform debate of 2009 (see also 7.8), industry representatives point out that drug expenditures account for only 10 percent of healthcare costs. Yet they make no reference to the reasons why this share has gone up.

6.4.3 Health Insurance and the Pricing of Prescription Drugs

Why do Americans pay a higher price on prescription drugs than anyone else in the world? The answer points to the core of the country's framework for medical politics: It is because of the fragmented, private-actor-centered healthcare market that has no unified oversight of drug costs. Governments in several other large pharmaceutical markets, notably in Europe such as France and Germany, place a restriction on the price for a particular drug. Others, such as the United Kingdom, impose a ceiling on the amount of profit that a company can earn from a particular medicine. And the majority of OECD countries apply external benchmarking of pharmaceutical prices in other jurisdictions to limit prices of drugs at home (OECD, 2008, p. 103). Unlike OECD countries with a national health insurance system, the federal authorities of the United States do not apply international comparisons or any other overarching mechanisms to control drug pricing. Instead, there is a patchwork of internal comparisons based on reference pricing at work, sometimes applied by private insurers, sometimes by the federal health programs, and sometimes by both. Despite a complicated network of regulations, these measures have not prevented the United States from having one of the highest prices – 30 percent above OECD average - for prescription drugs (OECD, 2008, p. 32). Ultimately, it is this absence of federal price controls in America's privatized healthcare that provides a comparative advantage for the biotechnology industry in the United States (claim 3).

As about two third of Americans have private health insurance coverage, the first look should go to the cost curbing measures of these actors. Many private health insurances have the prescription drug benefits for their members administered by so-called

pharmaceutical benefits management (PBM) firms. Some of the largest PBM firms represent several million insured individuals and have considerable market power. For PBM firms the most common cost cutting measure is charging differential co-payments for originator drugs and for generic versions. Another commonly applied cost-management tool, used by about half of US pharmaceutical benefits management firms, is a so-called therapeutic interchange (Hoadley 2005). It involves the dispensing of a chemically different, but cheaper, drug that is considered to be therapeutically equivalent in that it produces the same therapeutic outcomes and has a similar safety and toxicity profile as the original drug. In the United States, 90 percent of employees with private health insurance are in plans with a tiered co-payment scheme for generic, preferred and non-preferred drugs (ibid.).

By contrast, the power of the U.S. government to regulate prices is restricted to some federal purchasing schemes. Most importantly, the four largest federal government purchasers, the Veterans Health Administration (VHA), the Department of Defense, the Public Health Service, and the Coast Guard bargain with drug producers over a so-called 'Big Four Price' (Roughhead et al., 2007). These federal purchasing schemes limit the prices manufacturers can charge, using those obtained by competing private plans as a benchmark. Since most of these plans pool fewer patients than the federal purchasing schemes, which together provide coverage for about 20 percent of the U.S. population (OECD 2008, p. 98), this further fractioning of the demand side strengthens the bargaining position of drug companies.

In this context, the VHA is particularly relevant, because it is one of the largest healthcare systems in the United States[116]. Financed primarily through general taxation, the VHA is owned, operated and managed by the U.S. Veterans Administration. The VHA provides a range of health benefits to U.S. military veterans, including hospital, physician and prescription drug services. In 2006, 7.9 million veterans were enrolled with the VA health system. In addition, after a restructuring in 1997, the VHA also became the largest single U.S. purchaser of prescription drugs. Until 1997, the VHA operated on a decentralized basis, with weaker negotiating powers and larger price differences for certain pharmaceutical products purchased by different VA facilities (OECD, 2008, Fn 8, p. 118). After the consolidation of the VHA and the establishment of one single national formulary for prescription drugs, savings of 16 to 41 percent, depending on the drug class, could be achieved through shifts in prescribing behavior and price reductions from manufacturers (Blumenthal and Herdman 2000). Tendering of medicines to drug manufacturers played another crucial role in cutting the VA's costs for drugs too. The VA estimates, that between 1995 and 2003, national contracting of pharmaceuticals saved over $ 1.5 billion (Sales et al. 2005).

Medicaid, another important federal program, has no obligation for outpatient pharmacy benefits. Nonetheless, today all states have some outpatient pharmacy benefits and Medicaid spends over $34 billion on prescription drugs. To save costs Congress included in the Omnibus Reconciliation Act of 1990 (OBRA'90) the Medicaid Drug Rebate Program.

[116] Moreover, and somewhat paradoxical, nowhere does America's healthcare system come closer to the derogatory notion of 'socialized medicine' than in this service for the country's otherwise highly esteemed veterans.

This program requires pharmaceutical companies who wish their products be covered by Medicaid to grant the federal government a discount on outpatient drugs dispensed to Medicaid patients. Manufacturers must agree that the price charged to Medicaid will not exceed the Average Manufacturer Price (AMP)[117] reduced by a rebate percentage. The law then requires states to provide coverage of all FDA-approved medications made by manufacturers who have made rebate agreements (OECD, 2008, p. 99).

Yet Medicaid is an example for why federal structures, historically relegated to the second tier, have now become – willingly and unwillingly – a passive price-taker of what the private sector decides. Overall bargaining power is also tilted by the fact that U.S. public and private purchasers of drugs generally do not publicize the discounts they obtain from drug companies (OECD 2008, p. 143), which puts the latter in a more powerful position. To counter the corporations' bargaining advantage, states have entered multi-state rebate agreements for Medicaid with pharmaceutical companies. Yet there are also bilateral agreements between large pharmaceutical companies and states. A particular case is the arrangement struck between Florida and Pfizer. In exchange for having its key drugs included in Florida's preferred drug list to be reimbursed by Medicaid, Pfizer, instead of agreeing on a rebate, subsidized disease management and patient education programs (Bowe 2003). Moreover, there are drugs, such as the antipsychotic medication Zyprexa, for which 70 percent of sales go to government agencies and excluding that medicine form Medicaid's preferred medication list can render considerable savings for some states.

[117] The AMP is the price paid to a manufacturer for pharmaceuticals distributed through retail and mail-order pharmacies. This price excludes direct sales to federal purchasers.

In many cases, however, drug makers – using patients' advocacy groups that they fund themselves – wield sufficient power on state legislatures to protect their business from such cost cuts (Harris 2003).

Another side effect of the lack of an overarching federal pricing regime in the United States is that even if some public programs successfully negotiate a rebate from drug companies, pharmaceutical manufacturers compensate for it with an overall increase in prices. For instance, as a reaction to the Medicaid Drug Rebate Program, pharmaceutical manufacturers simply raised the comparative bar, namely the prices that they charged non-governmental wholesale purchasers[118]. This mixed outcome on drug costs of the Medicaid reform of the early 1990s is another example for how fragmentation of the market and no federal oversight of prescription drug costs in the American healthcare system made the American healthcare market prone to unprecedented hikes in costs for prescription drugs that benefited the makers of these products.

6.4.4 Struggles Around the Medicare Modernization Act of 2003

The question whether the government should have a role in drug pricing resurfaced a decade later in discussions about reforming Medicare. The VA restructuring demonstrated that a system with a single purchaser has greater power to obtain price concessions from pharmaceutical sellers. Yet in 2003, when Congress had to decide about legislation to reform Medicare and include prescription drug benefits, the opportunity for cost cutting by strengthening the bargaining power of the federal entity was deliberately foregone. Instead,

[118] According to a study of the Congressional Budget Office, wholesale rebates fell from an average of more than 36 percent in 1991 to 19 percent in 1994 (Congressional Budget Office 1996).

the adopted legislation outsourced the prescription drug benefits to private, competing, entities, each of which with a smaller basis than the whole pool of Medicare beneficiaries.

When Medicare was established in 1965, it was initially meant to provide health insurance to individuals age 65 and older, irrespective of their income or medical condition. The program was expanded in 1972 to grant coverage to people with permanent disabilities and individuals suffering from end-stage renal disease, and in 2001 to cover people with Lou Gehrig's disease. The growing share of the population qualifying for Medicare – from 9.2 percent in 1960 to 12.4 percent in 2005 (OECD 2007, p. 13) – was also reflected by increasing costs. By 2003, Medicare accounted for $244 billion, more than 11 percent of the entire federal budget (Office of Management and Budget (OMB) 2003, p. 40). Yet it had also become increasingly obvious that despite this hike in expenses, Medicare recipients were lacking one important aspect of healthcare coverage: Prescription drugs, which had been excluded from Medicare's original scope. At a time when drugs were cheap, Medicare recipients could pay for them out of pocket. Over time, however, the price hikes for prescription medicines affected this group disproportionately more. Due to their vulnerable health, Medicare beneficiaries – as of 2008, 38 million Americans age 65 and older, as well as 7 million people below that age with disabilities – are disproportionately heavier drug users too. Moreover, many Medicare beneficiaries live on modest incomes, relying on Social Security as their primary source of income[119].

[119] 46 percent of all Medicare recipients have an income below 200 percent of the federal poverty line ($ 20,800 per individual and $ 28,000 per couple, in 2008), and 38 percent of all Medicare beneficiaries live with three or more chronic ailments (Kaiser Family Foundation 2009, p. 3).

As mentioned earlier, one of the unresolved issues of the failed healthcare reform effort of 1993 was the question of prescription drug benefits for Medicare recipients. On December 8, 2003, President Bush signed into law the Medicare Prescription Drug Improvement and Modernization Act[120] (MMA). This Act, which went into effect in 2006, presented the most sweeping overhaul of the Medicare program since its inception. At an estimated price for the federal budget of $40 billion annually for the first ten years, the MMA added prescription drug benefits as a fourth category to Medicare (Part D)[121]. With more than 40 million Americans receiving Medicare benefits, pooling their needs for prescription drugs under one administrative roof potentially could have turned the federal government into the most powerful purchaser of drugs in the United States. And as the single largest buyer of drugs the government could have wielded its bargaining power to curb prescription drug expenditures for Medicare recipients. Yet influenced by the pharmaceutical and the biotechnology industry and as the result of a long and fierce political battle that will be described further below, the Bush administration and Congress chose otherwise. They followed the example of President Eisenhower mentioned above (see 6.3.1), who outsourced healthcare for federal employees to private plans and have the federal budget pay for it.

In this spirit, the MMA established competition among private prescription drug plans, in which Medicare recipients, paid for by federal monies, can enroll.

[120] Public Law 108-173.
[121] The other three parts are Hospital Insurance (A), Supplementary Medical Insurance (B) and Medicare Advantage Program (Kaiser Family Foundation 2009, p. 1).

Highlighting the sancticity of market-led competition, the text of the MMA explicitly stipulates the noninterference on the side of the Medicare administration:

> *"In order to promote competition…, the Secretary—*
>
> *''(1) may not interfere with the negotiations between drug manufacturers and pharmacies and PDP sponsors; and ''(2) may not require a particular formulary or institute a price structure for the reimbursement of covered part D drugs."*[122]

While federal subsidies encourage plan participation and better enrollee benefits, the individual plans negotiate drug prices with manufacturers to provide lower prices to plan beneficiaries. Such private prescription drug plans were estimated to save the average senior who, without drug coverage spent $1,285 annually on medicine, as much as $300 per year (Centers for Medicare and Medicaid Services 2005).

As of October 2006, almost 26 million Medicare recipients were enrolled in a Part D plan for prescription drugs. Plans vary widely in terms of the list of drugs covered, cost-sharing requirements, and requirements for prior authorization. Yet they are similar in that all of them still require considerable co-payment from enrolled Medicare recipients: For 2009, there was a $295 deductable and a 25 percent coinsurance up to the initial coverage limit of $2,700 for annual prescription drug costs. This is followed by a coverage gap ('doughnut hole') up to $6,154, which enrollees have to pay completely out of pocket. If the

[122] Public Law Public Law 108-173 [[Page 117 STAT. 2098]].

prescription drug requirements exceed this amount, enrollees pay 5 percent, the plan 15 percent, and Medicare the remainder (Kaiser Family Foundation 2009).

Despite its short life, some consequences of the MMA have already surfaced. As intended, Medicare recipients see their costs for prescription drugs reduced. Seniors who enrolled in a Part D plan for prescription drug coverage spent less than those who did not. At the same time, Part D offered less protection from high prescription drug costs than for instance employer plans or the VA[123], which do not have the MMA's 'doughnut hole' coverage restrictions. Government officials reported for 2006 that approximately 3 million of 23 million Medicare Plan D beneficiaries reached the point at which this gap in coverage occurred (Lee and Levine 2006). As importantly, the MMA has established a low-income subsidy mechanism for enrollment, but, since participation in Plan D is voluntary, particularly low income seniors seem to be foregoing coverage for prescription drug costs (Neumann et al. 2007).

Savings of about 4 percent in private spending for prescribed drugs were offset by an increase in public expenditures on prescription drugs, which rose from 2 percent in 2005, the year before Medicare Part D went into effect, to 18 percent in 2006. In part, this shift of burden had been intended. Yet overall, the Act did not turn around the cost increases caused by prescription drugs. In 2006, the year that the MMA went into effect, overall drug spending rose by 4.5 percent in real terms in 2006 after a 2.2 percent increase in 2005[124]. In

[123] A comparative study found that Medicare Plan D patients are paying almost 60 percent more for the top 20 drugs than veterans under their coverage by the VHA (No Bargain: Medicare Drug Plans Deliver High Prices 2007).
[124] See "Growth in health spending slows in many OECD countries, according to OECD Health Data 2008":

2009, Medicare Part D is expected to account for $61 billion – 50 percent higher than initially budgeted – and account for 12 percent of Medicare's total budget of $507 billion[125]. One study came to the conclusion that rather than cutting costs, the increasing role of private plans as a result of the MMA has led to cost increases of Medicare of about $11 million (Biles, Pozen, and Guterman 2009)[126].

Therefore, while the MMA did alleviate difficulties to obtain prescription drugs for senior citizens and people with disabilities, it did not solve the problem – neither individually, nor for society. Prohibiting the government from negotiating drug prices, the MMA, again, turned the government into a passive price-taker of whatever costs the makers of pharmaceuticals charge. How could such a 'giveaway to the drug industry' (Newhouse, Seiguer, and Frank 2007) happen? Taking off from the passage of the MMA, the next section will analyze the extent to which pharmaceutical and biotechnology influence the political debate about high drug prices in the United States.

6.5 Biotechnology and Pharmaceutical Industry's Interest Representation

Over the years biotechnology and pharmaceutical companies have built an effective machinery to represent their interests vis-à-vis political decision makers in Washington. Relevant for the arguments put forward in this study is not lobbying *per se*, but rather *on*

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http://www.oecd.org/document/27/0,3343,en_2649_33717_40902299_1_1_1_1,00.html, retrieved 5/18/2009.

[125] Prescription drug coverage under MMA's Part D will be largely financed (79 percent) through general federal revenues (Kaiser Family Foundation 2009, p. 16).

[126] The study also suggested that, instead of subsidizing private plans with federal monies, that amount had better been allocated to improve benefits for the low-income elderly.

which issues. The lobbying efforts and the political wrangling of biotechnology and pharmaceutical industries to shape the MMA in their favor reveal how relevant America's fragmented healthcare market without any federally invoked price cap has become for these businesses (claim 3).

How do these industries vent their positions and wield influence? Compared with other industries, pharmaceutical and biotechnology companies are not among the main contributors to electoral campaigns: Their total financial contributions for all federal elections between 1990 and 2010 amounted to $170 million, ranking only 17th and for 2008,[127] contributed $29.1 million to the election cycle of 2008, ranking only 20th. On the other hand, the pharmaceutical industry is the top industry with regards to lobbying efforts: From 1998 to 2009, pharmaceutical and health product companies, including biotechnology firms, allocated $1.6 billion to lobbying, $235 million in 2009 alone[128]. Another study, published by the Center for Public Integrity, concluded that pharmaceutical, medical device and other health product manufacturers almost tripled their lobbying expenditures between 1998 and 2007 from $67 million to $ 189 million[129]. While the top company listed is the biotechnology firm Amgen, among the top lobby spenders were transnational pharmaceutical companies headquartered in Europe, such as Roche, Sanofi-Aventis, and Novartis.

[127] These data do not distinguish between pharmaceutical and biotechnology industry. For example, the largest donor in this category was Pfizer, followed by Amgen. See http://www.opensecrets.org/industries/indus.php?ind=H04 (visited August 9, 2009).
[128] See http://www.opensecrets.org/lobby/indusclient.php?lname=H04&year=2010
[129] See http://projects.publicintegrity.org/rx/report.aspx?aid=985

This reiterates the centrality of the U.S. market for the destiny of the globally operating transnational pharmaceutical business.

Table 6.1: Pharmaceutical and Biotechnology Lobbying Expenditures 2007

Rank	Company/Organization	Amount (million$)
1	Pharmaceutical Research & Manufacturers of America	22.7
2	Amgen Inc.	16.3
3	Pfizer Inc.	13.8
4	Roche Holding AG	9.0
5	Sanofi-Aventis	8.4
6	GlaxoSmithKline	8.2
7	Johnson & Johnson Inc.	7.7
8	Biotechnology Industry Organization	7.2
9	Novartis AG	6.6
10	Merck & Co.	6.6
11	Bristo-Myers Squibb Co.	6.0
12	Abbott Laboratories	4.6
13	Eli Lilly and Co.	4.3
14	Boehringer Ingelheim	4.1
15	AstraZeneca Pharmaceuticals	4.1
16	Bayer Corp.	4.1
17	Genzyme Corp.	2.7
18	Wyeth	2.5
19	Teva Pharmaceuticals	2.3
20	Baxter Healthcare Corp.	2.2

Source: Center for Public Integrity.
http://projects.publicintegrity.org/rx/report.aspx?aid=985 (visited August 9, 2009).

In addition to individual companies, the above table also lists lobbying expenditures of interest group organizations: The Biotechnology Industry Organization (BIO) is the interest group organization of the biotechnology industry in the United States, and the world's largest biotechnology trade organization. It came into being in 1993, when two rivaling biotechnology trade associations merged: The Association of Biotechnology Companies (ABC), which represented mainly small start-up companies, and the Industrial Biotechnology Association (IBA), lobbying for more mature firms. To date, BIO has more than 1,200 members worldwide. Members include entrepreneurial companies developing a first product, Fortune 100 multinationals, state and regional biotechnology associations, service providers to the industry, as well as academic centers. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products[130]. BIO grew considerably over time, increasing its staff from some twenty to more than 150 employees and its annual budget from less than $3 million to over $52 million. Consequently, BIO has become a lobbying force in Washington to be reckoned with (Fox 2006). Similar to many other industry interest group representations, BIO has been headed by political insiders: Carl. Feldbaum, the BIO President from 1993 to 2005, had previously been chief of staff to Senator Arlen Specter (R-PA). Jim Greenwood, BIO's current president, had been a Republican from Pennsylvania in the U.S. House of Representatives from January 1993 through January 2005. As a senior member of the Energy and Commerce Committee, Greenwood was engaged in health care legislation, such as the MMA. Greenwood brought with him legislative experience as well as a new team of political insiders.

[130] See http://bio.org/

Predating the change in personnel, BIO's marching order for the Medicare reform debate was already adopted in 1999:

> *"BIO strongly believes that pharmaceutical benefit options should be offered to beneficiaries in the context of an overall, market-based reform of the Medicare program… BIO believes that Medicare benefits - including coverage for prescription drugs and biologics - should be delivered through a decentralized, pluralistic market structure that encourages meaningful competition in order to preserve patient choice, improve quality and encourage innovation. Government regulation should be limited and market-based delivery mechanisms should be utilized. Explicit or indirect price controls that stifle innovation must be avoided."* (BIO 1999)

Consequently, BIO lauded the passage of the MMA in 2003 as its "*most significant legislative victory to date,*" because the Act included BIO's market-based principles. Moreover,

> *"[p]assage of this historic legislation marked the culmination of more than four years of federal government relations, grassroots and communications efforts."* (BIO 2004)[131]

[131] Its successful lobbying strategy is summarized in another BIO publication, which has the telling title: "*The Measure of a Great Industry is Who's Listening."(BIO 2003)*

The real prize for pushing the MMA through Congress, however, does not go to BIO, but to the pharmaceutical industry and their trade organization, the Pharmaceutical Research and Manufacturers of America (PhRMA)[132]. PhRMA is much smaller in membership than BIO, but its 31 member corporations and 20 associate members comprise all the leading global pharmaceutical companies, headquartered in the United States and elsewhere[133]. Irrespective of their representation through BIO, a number of large biotechnology firms, such as Amgen, Genentech, and Millennium Pharmaceuticals, are also a member of PhRMA. Pharmaceutical companies initially would have preferred having no Medicare prescription drug legislation at all. Yet increasing public concern made them change tactics. Instead of blocking legislation wholesale, pharmaceutical companies tried to influence the legislative process in such a way that the law adopted would increase prescription drug access without government price controls (Stolberg and Harris 2003).

This became more possible after the 2002 election led to a Republican majority in both chambers of Congress. Influential Democratic healthcare legislators such as Edward Kennedy saw their hopes for a federally run prescription drug plan dwindling. Nevertheless, negotiations in 2003 still had Senate and House of Representatives present bills with significant differences. Under the Senate bill, the federal government would provide prescription drug coverage in any region where fewer than two private insurance plans were available.

[132] See http://www.phrma.org/
[133] In fact, in April 2009, PhRMA elected the CEO of the Anglo-Swedish multinational drug company AstraZeneca, David Brennan, as board chairman.

The House bill prescribed the government pay subsidies to private insurers to induce them to offer coverage, but would not directly provide such coverage itself. Throughout these negotiations, Congressman Billy Tauzin, (R-LA), became a vocal opponent of government involvement in Medicare reform[134]. Tauzin shepherded his views for the 2003 Medicare drug bill first through the House-Senate Conference and later through the House of Representatives[135]. Tauzin was criticized for leaving the House of Representative to become the head of PhRMA, yet he was not the only one engaged in this bill who left public office for private industry. For example, Thomas Scully, Administrator of the Centers for Medicare & Medicaid Services (CMS), and the administration's lead negotiator for the MMA, left his government job ten days after the MMA was signed to become a Senior Counsel at Alston & Bird, a lobbying firm where he is focusing on health care regulatory and legislative matters. At least 15 congressional staffers, congressmen and federal officials who were involved in ushering the MMA through Congress subsequently left government for the pharmaceutical and biotechnology industry.

While lobbying efforts and revolving doors may come as no surprise to Washington observers, they are relevant in this context, because they point to the crucial role that price controls have come to play for the *modus operandi* of the biotechnology and pharmaceutical industry. The MMA is another example for why laissez-faire solutions are *never* inevitable or natural outcomes, but *always* politically fabricated.

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[134] He scolded the Democrat's vision of Medicare as *"the government does it all…The government provides the benefits, and no one else—no competition, no reform."* (Quoted in Pear (2003)).

[135] For a journalistic account of the longest roll call in the history of the House of Representatives see "60 Minutes: Under the Influence", April 1, 2007: http://www.cbsnews.com/stories/2007/03/29/60minutes/main2625305.shtml

By giving preference to a private solution instead of an overarching public effort, American politicians once again paid tribute to neoliberal ideology. But as the MMA has not averted crises of accessibility or rising healthcare costs, the saga of healthcare reform and drug pricing inevitably continued into the next electoral cycle (see 7.8).

6.6. Conclusions

In international comparison, the healthcare system of the United States is exceptional in a number of ways: The country allocates more resources to health than any other wealthy nation, but it does so in a way that relies predominantly on private insurance coverage. Federal programs for particularly vulnerable groups of society, such as the elderly and people with disabilities, have not turned into a Trojan horse for 'socialized medicine'. On the contrary, a division of labor according to which federal healthcare is limited to those individuals generating the highest costs, manifested the preeminence of private health providers.

This provision of healthcare by the American variety of capitalism has turned into a comparative institutional advantage for pharmaceutical and biotechnology industry in the United States. Whereas all advanced industrial nations face the challenge of how to mediate between healthcare needs and costs, the United States is the only country in which politicians deliberately and repeatedly opposed state regulation and granted the market the upper hand. Since a national system for healthcare was not included in the Social Security legislation of the New Deal, after World War II healthcare became highly dependent on

private employment-based private insurance. Additional federal programs, starting with President Eisenhower's health insurance for federal employees, and especially Medicare and Medicaid, all outsourced the provision of healthcare, either partially or completely, to private actors and relegated the public hand to paying the bill afterwards.

The evolving healthcare system with its division of labor between the private and the public created an incentive structure most favorable for pharmaceutical and biotechnology companies. Unlike other wealthy countries with a national health insurance system, in the United States there is no central agency or policy in place to control prices for healthcare services and products, including drugs. Instead, by limiting the role of government, a patchwork of reference pricings is applied, sometimes by private insurers, sometimes by federal health programs, sometimes by both. The whole healthcare system of the United States can best be described as the private sector being the price-setter, whereas the public becomes the price-taker. What market advocates see as a blessing, more competition among private actors, has worked out the opposite way: With private health insurance in the drivers' seat and public health provisions as a sidekick, prescription drugs are more expensive than in most industrialized countries, while more than 40 million citizens remain uninsured today.

The institutional setup of healthcare provision has profited the biotechnology and pharmaceutical industry. Yet beginning with President Clinton's failed proposal to overhaul healthcare, these industries were able to influence reform efforts according to their industry's needs. Instead of arguing for an extension of coverage for all Americans,

accepting lower prices for more patients, so far pharmaceutical and biotechnology companies have opted for a limited scope of coverage with less regulation of prices by public authorities. Following through on this strategic and ideological roadmap, pharmaceutical and biotechnology industries' political leverage was instrumental for the making and passing of the Medicare reform bill that outsources prescription drug benefits to private insurances.

By advancing an agenda of market-led solutions for public health needs, these industries both profited from and exacerbated a neoliberal political *zeitgeist*. However, with a global economic crisis ongoing, neoliberal laissez-faire policy prescriptions have lost their hegemony. The current market-based healthcare system in the United States can no longer be taken for granted, not in the least because corporations have identified the competitive disadvantage that an employment-based system presents for them. At the time of writing it is not clear whether or not reform efforts of a new administration under President Obama will succeed. If so, it will most likely fall short of a comprehensive overhaul of American healthcare. Yet pressure on the current practice of prescription drug pricing in the United States, and, in its tailwind, the business prospects of the biotechnology industry, will almost certainly increase. The next and final chapter will therefore address these and other challenges to the blockbuster drug regime and its consequences for the biotechnology industry.

Chapter 7: Side Effects of America's Biotechnology Innovation Regime

> *"The biggest risk facing the biotech industry is the prospect of increased price controls and access regimes – a risk that could threaten the survival of the industry…High prices, especially in the US market (the last major market entirely free of price controls) makes biotech innovation possible. The possibility of price controls in the US, plus the escalating cost of development would change this paradigm forcing the sector to seek new development strategies or to invest less in R&D."*
>
> (Ernst & Young, Strategic Business Risk: Biotechnology 2008, p. 6)

7.1 Introduction

This study made the following claims: *First*, a biotechnology revolution has not taken place so far. Instead, the creative destruction that characterizes the biotechnology industry has been co-opted by the pharmaceutical industry's blockbuster drug logic. *Second*, the history of political interventions of the U.S. government has led to a clustering of the biotechnology industry in certain regions in the United States and to a competitive advantage for the biotechnology industry located in the United States vis-à-vis other countries in general. Politics to stimulate economic competitiveness trump free-market rhetoric. *Third*, as part of America's market-driven healthcare system, the absence of federal controls over prescription drug prices is a crucial comparative advantage for the biotechnology industry in the United States.

In this concluding chapter, I will first recapitulate some of the main findings from the interviews with corporate actors as they relate to these three main claims (7.2). Subsequently, I will discuss a number of ramifications that the current biotechnology innovation regime in the United States has. I will first focus on stem cell research, biotechnology's latest harbinger of hope for tailor-made human medicines, which seems to play out a number of the same dynamics that characterized the ascent and decline of genomics (7.3). Two consequences of the current market-driven innovation regime cannot be addressed in-depth here, but are too important to be left out. These are respectively the side effects of the increasing commodification of knowledge production (7.4), and the hegemonic position that the United States could obtain thanks to globally binding legal mechanisms (7.5). I will then go back to the core of the current market-driven model in which biomedical innovation is occurring in the United States. First I will take a more theoretical look on the evolving relationship between the biotechnology and pharmaceutical industry, which also revisits the question of how revolutionary the effects of biotechnology for medicine indeed have been (7.6). Next I will address the increasing political pressure in the United States on the economically successful blockbuster drug model. Irrespective of the impact of biotechnologies on developing new drugs, large pharmaceutical companies have turned into highly sophisticated marketing machineries (7.7) Subsequently, the most recent efforts to reform healthcare in the United States will be scrutinized for the role and position that the biotechnology and pharmaceutical industry play in it (7.8). The chapter will conclude with an outlook for the biotechnology innovation regime in the United States at a time in which the hegemony of neoliberal, free-market policy prescriptions can no longer be taken for granted.

7.2. Biotechnology Innovation Regime in the Eyes of the Biotechnology Actors

Throughout the interviews, it became apparent that in many ways, the biotechnology and pharmaceutical industries are not completely different, but rather complementary. A clash of organizational culture between old, sclerotic, bureaucratized Big Pharma and new, nimble, and nifty biotechnology firms is part of the latter's gospel. Past cultural clashes became virulent throughout the interviews for instance, when biotechnology actors reported on the exodus of staff after being taken over and integrated into the hierarchy of Big Pharma. Today, large pharmaceutical firms generally have become more hesitant to integrate fully an acquired biotechnology firm. Large drug companies do not want to destroy the value for which they paid so dearly and instead manage their biotechnology acquisitions at arm's length. As a result of the often mentioned vivid exchange of human resources among both industries – some caused by mergers and acquisitions, others by the life cycle of companies – there is not so much talk about clash, but rather conversion. In this regard, there is no difference whether the buyer is an international or an American company. Moreover, there is also the conversion among large pharmaceutical companies themselves. Corporations such as Pfizer, GlaxoSmithKline, and Roche all try to emulate the innovative nimbleness of biotechnology companies by splitting up in-house R&D into competing clusters of innovative excellence.

Yet a clash, albeit less over culture but over business models, did indeed occur at the end of the 1990s. For a while genomics companies appeared to turn the table of the drug development regime. Multinational drug companies heavily invested into companies that

seemed to own the Holy Grail for drug development, only to discover that the way towards gene-based medicines was much more arduous and unpredictable than initially proclaimed. Big pharmaceutical companies started reconsidering their approach towards genomics after the litigations against the drug Vioxx, which almost bankrupted its producer Merck. Vioxx turned lethal because it was marketed to a much larger population than medically reasonable. Whether or not in the future such malpractice will be prevented by genomics or by a different marketing practice remains to be seen. In any event, there is a lesson to be learned from genomics about the contradictions between scientific and business imperatives that will be worthwhile remembering when taking a look at biotechnology's most current hope: Stem cell research.

The interviews also highlighted an important twist in the division between research 'for profit' and 'not-for-profit'. Scientific development relevant for the biotechnology industry was facing a dilemma: On the one hand, scientific advancements require the free exchange of ideas. Cutting-edge research in particular depends to a large extent on tacit knowledge, which is not readily transferable via codified sources. And the more certain knowledge becomes tacit, the more does its transfer depend on personal, face-to-face-interaction. Biotechnology companies wanting to profit from the exchange of tacit information therefore want to be present in clusters with a lot of 'free buzz'. These informal rather than contractual exchanges point to an important limitation of the VoC approach for understanding the biotechnology industry. VoC suggests the dominance of contractual, market-based coordination in a liberal market economy such as the United States. It cannot

explain how companies in the surveyed clusters enjoy a comparative institutional advantage by being immersed in a cluster with tacit knowledge.

At the same time, while everybody wants to profit from the free-floating of ideas, the willingness to provide it is decreasing. Even if people do meet in person, sharing of knowledge – tacit or otherwise – becomes less likely when individuals or entities such as universities or companies are entitled to exclusive ownership of such knowledge. Intellectual property therefore not only becomes a bargaining unit based upon which businesses are funded, but it becomes also a roadblock. In this regard, the transformed role of universities turned out to be particularly consequential. Traditionally seen as institutions whose primary purpose is to generate knowledge for the larger public good, universities have become increasingly motivated by the protection of intellectual property and the collection of licensing fees for their inventions.

While academic research is now often conducted with profit considerations in mind, conversely, a vast amount of biotechnology research is carried out by companies that will never make a single penny of profit. For those companies that 'burn' money, adding long-term value is more important than short-term profitability. This loss-making process can be perpetuated for as long as some investor continues to add fresh money, speculating on a future value that will earn him a huge enough profit. Ultimately, the boom and bust cycles of the biotechnology industry are an example that in every speculative process, a realignment of expectations and reality leads to the destruction of a lot of capital. Sometimes the destroyed capital is fictitious, sometimes not, and both processes contribute

to the restructuring of the industry. Creative destruction also means that, while some companies may be going out of business, others merge, and people who created the knowledge move on and may start elsewhere. People engaged in the biotechnology industry are fully aware that, where there are some big winners, there are normally a lot of small and big losers. While taking the risk of being at times one of the latter, the ultimate aim is of course, to be part of the former.

The interviews also pointed to the ambivalent functions that the neoliberal state has to play. Neoliberalism does not deny a role for the state, but rather, asks for a state being more active in some respect, while being hands-off in others. For the majority of interview partners laissez-faire equaled governmental pro-market intervention. Many biotechnology industry representatives, while on the one hand demanding that the state stay out of their business, on the other hand highlighted the importance of US federal intervention for the wellbeing of the industry. Whereas small companies appreciated the support provided by NIH and other federal SBIR grants companies closer to a marketable product worked towards a favorable verdict by the FDA. As it turned out, the sum of federal 'enabling policies' on access to capital, particularly venture capital and intellectual property rights, were more important than the actual level of direct subsidies.

Clustering also reflects the inbuilt contradiction of the neoliberal state being pro-active active in some respect, and hands-off in others. Clusters are not only in competition with each other, but they also have their individual strengths and weaknesses. Many interviewees pointed out the fact that regions with a vibrant biotechnology industry always

have other advantages as well. Successful biotechnology clusters allow the industry to profit from cross-industry and institutional interconnections. For example, San Francisco has the information technology industry of Silicon Valley, San Diego the military industry, Boston the agglomeration of the most prestigious research universities, and Maryland federal institutions such as the NIH. These linkages and competitive advantages had to do with a path dependence of past politics and specific policies 'to make the peaks higher'. And while biotechnology actors expressed their willingness to take advantage of such policies, they are not really acknowledged as playing a steering role in the allegedly free market competition.

Lastly, but most importantly, free-market competition and non-intervention are most vocally claimed with regards to prescription drug pricing. As the interviews illustrated, the biotechnology industry acknowledges that the American healthcare system enables them to charge premium prices for prescription drugs. While all these corporate activities make sense from the viewpoint of the individual companies, the question again is what are the consequences for society at large? How has, for example, the ascent of the biotechnology industry affected the drug development process? I will try to answer these questions in section 7.6 below. Yet I will first zoom in on some other consequences of the market-driven innovation paradigm for biotechnologies: Stem cell research; the commodification of biomedical sciences; and the global dissemination of the United States' paradigm by legally binding treaty bodies.

7.3 The Future of Stem Cell Research

There is an important lesson to be learned from genomics also for biotechnology's latest promising scientific advancement: Stem cell research. On the one hand, these techniques have raised hopes that this new line of investigation will lead to therapies and, ultimately, cures for an array of diseases from Alzheimers to Diabetes to Parkinsons. On the other hand, there has been a broad discussion about ethical implications, particularly of human embryonic stem cell research (Holland, Lebacqz, and Zoloth 2001), as well as the regulatory criteria under which the administration of President George W. Bush provided federal funding for such research (Lehmann 2001). Half a decade later, and tainted by the scandal of a South Korean researcher who fabricated data on cloning human embryonic stem cell lines, the question remains: How beneficial will stem cell research be? In the United States, in absence of an overarching federal support program, several states have taken the initiative to provide funding[136]. By far the most comprehensive support is being marshaled by California, which, in 2005, passed Proposition 71 to create the California Institute for Regenerative Medicine (CIRM). Financed by issued state bonds, the state will distribute nearly $300 million annually in stem cell funds for 10 years to California universities and research institutions. In contrast with earlier biotechnology-related exuberances, this time, protagonists have made sure not to oversell the expectations (Longaker, Baker, and Greely 2007). Researchers agree that there is still a lot of scientific legwork to be done before there will be approved therapeutic procedures and that this new

[136] These are, among other, New Jersey, Wisconsin, and Massachusetts. For an overview see Johnson (2006).

approach is at least one or two decades away from widespread commercial application (Cookson 2009).

Stem cells offer a variety of different treatment options, and particularly when derived from an individual's own body, bear the potential for tailor-made therapies. Similar to genomics this would again be in conflict with the blockbuster drug model. It is therefore noteworthy that also large pharmaceutical companies have started to invest in stem cell research. For example, in 2008, Pfizer launched an independent research unit 'Pfizer Regenerative Medicine', focused exclusively on using stem cells to develop new medicines. Endowed with more than $100 million over the next 3 to 5 years, one of the first deals signed was with the Wisconsin Alumni Research Foundation (WARF) in Madison, Wisconsin. The deal allows Pfizer to license WARF's human embryonic stem cell patents for the development of new drug therapies. Previously, GlaxoSmithKline (UK) had signed a $25 million four-year deal with Harvard University, and the venture funds of the Swiss multinationals Novartis and Hoffman-LaRoche founded a Spanish company testing stem cells (Siva 2009). While the feasibility of individualized treatment based on stem cells remains to be seen, for the time being Big Pharma's engagement in this new field of science are geared towards more short-term, tangible aims, such as applying stem cells for drug testing. Science is important, but as it was the case with genomics, the successful introduction of new biotechnologies does not depend so much on their scientific potential but rather on their potential to be molded into a marketable product. This makes it more likely that also stem cell research would rather be co-opted to become an integrated part of the value-added chain for drug development, and not an alternative approach towards

medicine. And while stem cell research received a short-term boost when President Obama's Executive Order of March 2009 liberalized the conditions for federal stem cell funding, the calculations of the most prominent market actors, such as Big Pharma and VC funds will be far more consequential for the long-term prospects of these new techniques.

7.4 Scientific Knowledge as a Commodity: The Tragedy of the Anti-Commons

In this study, intellectual property rights have been highlighted on various occasions: Actors from the biotechnology industry in chapter 4 explained the relevance of patents for the business models they pursued. And chapter 5 described how a strong and elaborated intellectual property regime has become a signature of the American neoliberal state. Legal and political strife occurred on a number of occasions when relevant factions, for instance within the scientific or the business community, contended that the United States' patent regime for biotechnologies was overreaching. This was for instance the case with the patenting of unspecified sequences of the human genome. In the following, such concerns will be deepened and brought to a more systemic understanding of the commodification of knowledge.

There are good reasons to believe that the reality of academia has never lived up to a Mertonian, normative notion of science as being untainted by other than scientific factuality[137].

[137] See for instance Jasanoff (2005, p. 228).

That idyllic situation may not even have occurred during the 'Golden Age' of Post-World-War II research, when many biomedical scientists were engaged in basic, not-for-profit research that received constantly increasing federal resources, for instance to win the 'War on Cancer'. But even if academic research was indeed locked up in the ivory towers of America's institutions of higher learning, the Bayh-Dole Act of 1980 and related legislation to promote the commercialization of research changed this for once and all. As intended, the Act fostered commercialization of academic research, but it also had some unintended side effects.

In 2003 alone, American universities earned $1.3 billion from patented research (Anonymous 2004). The top tier of patented biotechnologies generate double if not triple digit millions of dollars in annual licensing fees[138]. Some see entrepreneurialism as a general proof of for success of the American research university (Crow and Tucker 2001). For others the adoption of economic development as main part of universities' mission elevated academic institutions from 'secondary' to 'primary' importance (Etzkowitz and Leydesdorff 2000). But while this 'entrepreneurial' university is contested within the academic community for reasons that hark back to the Mertonian ideal (Krimsky 2003), it is also criticized by corporate actors for different reasons. For instance, some of the interview partners from the private sector complained about the inaccessibility of research universities' technologies because of their rigid IPR management. Criticism is not only related to spinning off technologies into the for-profit sector. Already in the late 1990s, the

[138] In 2006, the most profitable single technology deal, worth $157 million, was New York University's licensing agreement for the blockbuster drug Remicade with Centocor and Johnson&Johnson (Lawrence 2008).

NIH complained that the ways universities guard their intellectual property are endangering the free exchange of basic research tools. Universities, the NIH contended,

> *"have no duty to return value to shareholders, and their principal obligation under the Bayh-Dole Act is to promote utilization, not to maximize financial returns."* (quoted in Press (2000))

In general, the proliferation of ownership claims threatens to stifle the free exchange of ideas. While every individual actor wants to profit from the 'buzz' of tacit, publicly funded, and freely available knowledge, nobody wants to create it. Corporate guidelines prohibit the exchange of ideas that may be proprietary. And companies do not apply for federal grants, because they fear that the peer review process would disclose proprietary information to their competitors. One rather unintended consequence of the increase in proprietary knowledge seems to be that it undermines a characteristic strength of biotechnology clusters: Knowledge spillovers due to close geographic proximity. What is at work here is the 'greed gene' in reverse: Unlike the 'tragedy of the commons' (Hardin 1968), which explains why people selfishly overuse shared resources, the ongoing proliferation of intellectual property rights in biomedical research has created a 'tragedy of the anti-commons': Too many owners can block each other so that resources (knowledge) become under-utilized (Heller and Eisenberg 1998).

Proprietarization of basic research in universities has contributed its share to this tragedy of the anti-commons. Yet this is not the only side effect that the promotion of economic self-

interest has within the current pharmaceutical innovation regime. For example, it is by now well documented how the influx of corporate monies into academic biomedical research, such as the clinical testing of drugs, has led to conflicts of interest (Angell 2009). Meta-analyses of drug efficacy studies found that research funded by pharmaceutical companies were more likely to have outcomes in favor of the sponsors than studies that were funded otherwise (Lexchin et al. 2003). The academic literature is biased towards studies that prove drugs efficient, also because reporting failures is not in the interest of corporate sponsors (Kondro and Sibbald 2004).

Also, the results of heads-on-comparisons between similar but different treatments, for instance with different me-too drugs, are generally not publicized. Such comparative trials are too costly to be funded out of existing institutional budgets. Pharmaceutical companies, while having an interest in such comparisons, have no incentive to publish the results about their copycat drugs' efficiency (or lack thereof). Drug firms therefore increasingly redirect expenditures from academia to CROs and have such comparisons carried out confidentially. CROs not only promise to save costs, but they provide various types of fee-for-service research and have become firmly established within the transformed global drug development architecture. Most importantly, conflict of interest may be an issue for academic institutions, but it is not for CROs. They are predominantly concerned with delivering a service on time and under budget.

The way CRO's manages a clinical trial for its client – normally a biotechnology or a drug company seeking for regulatory approval – is to subdivide the trial in a way that allows the

client to pick and choose among the most favorable outcomes. And since the information derived from such testing is proprietary, the larger scientific community will not be able to learn from the failures. Finally, on behalf of drug companies CROs are conducting a number of post-approval (Phase IV) studies on drugs, which are often times thinly veiled marketing efforts to get physicians used to prescribing these medicines. CROs illustrate that the problem of knowledge commodification is not limited to for-profit research and the infringement of this principle into the academic sphere. Rather, CROs are an indispensible part of the current innovation regime with regards to the drugs that are produced, the scientific knowledge that is not produced, and the marketing that is pursued. In this sense they exemplify the *"structural consequences of a wider commercialization imperative"* (Mirowski and Van Horn 2005, p. 514) of neoliberal policy provision. My study focuses on the United States and highlights how the imperative of market mechanisms works along the entire innovation process, from the beginning of scientific research until the end, when a drug is sold at a certain price. Given the preeminent position of this country in the global political and economic order, the innovation system has important consequences also beyond the United States, to which I will turn next.

7.5 The Power of Patents and Markets

To make knowledge a tradable commodity requires not only a sophisticated toolbox on the inside of a nation, challenges are even bigger when these intellectual achievements are supposed to be traded transnational. Also in this sense, as part of the neoliberal awakening America's state has been by no means a hands-off, but interventionist for the sake of promoting economic activity. Throughout the 1980s, the lobbying efforts of a dozen

transnational corporations, among them Pfizer, Monsanto, and Merck, became instrumental for implementing intellectual property protection within the ongoing Uruguay Round of the General Agreement on Trade and Tariff (GATT). Aided by European and Japanese industry representatives, these corporations were able to formulate an agenda to modify international law to protect their markets (Sell 2003). Thanks in part to the 'revolving door' between the corporate and political sphere, the U.S. government acted as the most forceful representative of these corporate interests, so that an Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was included when the World Trade Organization (WTO) was established as the outcome of GATT in 1994. Countries seeking WTO membership to gain access to global markets also had to abide by the TRIPS stipulations for intellectual property protection. As a consequence, the bar for intellectual property protection on the global level increased considerably. Especially developing countries were forced to implement domestic IP systems for a number of previously unregulated goods, such as plant species and medicines, which are crucial for the biotechnology industry. TRIPS has a multi-tiered timeline for implementation for industrialized, developing, and least developed countries and countries could include in their IP legislation various exceptions to patentability. Yet such technicalities become hard to manage for underfunded state bureaucracies. Consequently, the new intellectual property protection regime has become a contested issue, both on the theoretical and on the practical, political level.

As comparative studies of intellectual property rights illustrate, over the course of history, countries that try to catch up with technological development have always preferred a lenient IPR system, whereas those at the forefront of technology aimed at rigid

enforcement of protecting their inventions (Chang 2001). Also the United States changed tack, and today coerces developing countries to fulfill a standard that was not even remotely observed when the United States was at the similar, or even more advanced, stages of development (ibid., p. 293). But while throughout the 19th century, protection of intellectual property was considered incompatible with the idea of free trade, at the end of the 20th century, a paradigm shift occurred so that intellectual property became a central component of free trade. (Sell 2003, p. 186). Critics point out that despite the rhetoric of trade liberalization, the consequence will be a new mercantilism. Instead of preserving domestic markets for infant industries, it protects global markets for the owners of innovations in advanced technologies (Bifani 1989, p. 177).On the other hand, advocates of international IP agreements argue that developing nations would receive more foreign direct investment and technologies (see for instance Maskus (2000)).

As a result of the leading role of the United States in multilateral regulation after 1945 as well as the hegemony of American trade negotiators in international forums, the United States managed to imprint its domestic understanding of IP protection on the international order established by TRIPS (Sell and May 2001, p. 485). Seen this way, also internationally the formation of patent laws and IP regimes should be read as a legalized way of congealing for a certain period the political struggles about technological progress (see 5.6). Also internationally therefore, constellations of political power are not set in stone and remain contested: Throughout the current round of negotiations on trade liberalizations, which started in Doha, Qatar in 2001, developing nations became more organized around issues such as access to medicines and overriding patent protection in

cases of national health crises. In August 2003, WTO members approved a decision that offered an interim waiver under the TRIPS Agreement. It allowed a member country to export pharmaceutical products made under compulsory licenses to least-developed and certain other countries (Fergusson 2006, p. 16). As the Doha round collapsed in 2008 on the issue of farm subsidies, there is currently no momentum for further alleviation of patent requirements within the WTO regime. Nonetheless, the heightened self-confidence of emerging global players such as China, India, and Brazil, as well as the increasing consciousness of a global non-governmental audience, make it highly unlikely that international trade negotiations will ever again be high-jacked by a self-select group of business interests that led to the original TRIPS Agreement.

In part, this new political constellation is also the result of a number of high-profile backlashes against pharmaceutical companies that tried to extend their intellectual property protection in developing countries. For instance, when in 1997 the South African government made it legal to import anti-retroviral drugs from cheaper, generic sources, about three dozen pharmaceutical companies jointly filed a lawsuit against the government, stipulating that this so-called parallel importing was in violation of South Africa's obligations under TRIPS. Due to the public, global outcry, the pharmaceutical companies decided to drop the lawsuit in 2001, but the damaging image of an industry that is hugely profitable while ignoring people's welfare remained (Ceccoli 2004, p. 134).

The problem of drugs for developing countries is, however, only in part a question of making them affordable at lower prices. Given the market imperatives that large

pharmaceutical companies follow, drugs are developed for US and Western markets, not for diseases of poor countries. Less than 10 percent of the worldwide expenditure on health R&D is devoted to the major health problems of 90 percent of the global population. There is an obvious lack of market incentives to develop drugs against diseases such as malaria, tuberculosis, sleeping sickness, and dengue fever. New models for R&D, such as public-private partnerships and virtual drug companies try to rectify this deficit and rally financial and scientific resources, including biotechnology (Lehmann 2001). Most of these approaches transfer resources from the industrialized to the developing world and many are funded by philanthropic donors. Some, such as those funded by the Bill and Melinda Gates Foundation, deliberately apply the metrics of the for-profit world to the non-profit sector. Yet as the public health system in many countries had been systematically dismantled by decades of neoliberal structural adjustment policies, 'venture philanthropy' interventions looking at short-term, quantifiable outcomes may not find the necessary absorptive capacity.

Globally, the unequal access to drugs and medical treatment are the most drastic proof for how the biomedical innovation regime based on market principles has gone awry. Even more than on the national level, in absence of an overarching authority private entrepreneurial activity remains insufficient to fulfill broad health needs. Solutions are therefore even more complex than simply re-instating previously dismantled state capacities. Domestic scientific capacities would have to be built, but this only makes sense when accompanied by measures, such as reversing a global brain drain in health workers (Garrett 2007). Reinvigorating a global public health agenda would mean a comprehensive

shift away from a neoliberal paradigm intrinsically geared towards supply-side driven, proprietary technological development. As biotechnology so far predominantly evolved within the ideology of 'product' solutions for complex societal problems, it remains to be seen whether the technologies could be used productively also under a different paradigm.

7.6 Revisiting the Relations Between Biotechnology and Pharmaceutical Industry

Research on effects of the ascent of the biotechnology industry for the innovation regime in drug development has led to inconclusive outcomes as for the overall gains. For instance, a study by Lichtenberg (2006) looked at the effect of creative destruction on drug development. While not distinguishing between biologically derived and other drugs, it was found that in the United States there is a highly significant positive relationship between new priority drugs[139] and the mean age at death. Looking at how creative destruction may have promoted the development of new drugs, the study found that pharmaceuticals that improve available therapies expand the total market of that therapeutics class. By contrast, drugs whose therapeutic qualities are similar to those of already marketed pharmaceuticals mainly reduce the sales of the already marketed product. Finally, sales of old drugs are reduced much more if new drugs are introduced by firms that have previously invented drugs in that class than by drugs from firms not yet present in that market. The findings of the study, however, are limited as the variation observed may be a result of marketing.

[139] These are drugs that the FDA considers to represent an advance over already available therapies.

Moreover, Lichtenberg's study covers a time, (1970-1991), during which the biotechnology industry had few marketable products.

As for marketable products, direct comparisons and gains from biotechnology drugs are hard to come by. It has been argued that if there were more examples like Genentech's recombinant human insulin, which substituted a similar substance produced differently, such head-on competition with Big Pharma would likely have a socially beneficial effect (Cockburn 2004). Biotechnology's most tangible outcomes are the biological drugs discussed in chapter 2 (see 2.9). Biologics are even more expensive than other blockbuster drugs, and while some pharmaceutical companies struck marketing deals with biotechnology firms to exploit the potential of biologics, the segment is currently limited to 15 percent of the U.S. prescription drug market.

The vast majority of biotechnology companies function as a sub-industry in which different parts compete with one another. As a result of the restructuring of pharmaceutical R&D, hierarchical in-house research has given way for an increased upstream competition between different providers of technologies, processes, and therapeutic compounds. Drug firms have embarked on various ways of collaborations with small companies, many of them biotechnology firms, to fulfill specific tasks along the way of the value-added chain from scientific discovery over drug development, clinical trials, regulatory approval, and marketing. The new layer of biotechnology companies, many of them focused on only one molecule or technology, are a typical example of diversification and outsourcing of risk that is also characteristic for post-Fordist industrial production. Nightingale and Mahdi

(2006) therefore argue that the effect of biotechnology is not that it radically changes industrial organization, but that it contributes to

> *"a Toyota-style knowledge supply chain, where a range of diverse technologies and leads are generated in small biotechnology firms, focusing on very uncertain and potentially problematic technologies. When the uncertainties are reduced, large pharmaceutical firms bring them in-house to expand their capacity utilization."* (p. 104)

Therefore, despite having been proclaimed time and again, so far there has been no 'biotechnology revolution'[140]. Yet the more competition in drug development is shifted upstream (and, ultimately, into the sphere of academia), the more resources are wasted on bargaining and transaction costs (Cockburn 2004, p. 19). This inflates the entire R&D value-added and drug companies that decided to re-organize their R&D architecture have to live with high uncertainty about what type of upstream R&D activity will ultimately be useful. The fear of 'missing the boat' induces them to invest in a variety of technologies, and, contributing to hypes around certain technologies, will overpay for many of them that do not realize added value as expected.

This was for instance the case for big pharmaceutical companies' huge upfront investments for research collaborations with genomics companies in the late 1990s. From the beginning, there was something paradoxical about large pharmaceutical companies'

[140] Nightingale argues that other indicators notwithstanding, the claim proved attractive to be picked up by politicians who promised development and economic growth, on the regional and the national level (2004, p. 567).

investment in the results emanating from the sequencing of the human genome. Understanding the genetic bases of diseases could in theory create the opportunity to ‘personalize’ medicine, including drugs. Drug treatments would then be customized according to individuals’ genetic predisposition. As drug development becomes more targeted, it should advance improved therapeutics. At the same time, however, and as a logical consequence, therapeutic markets would fragment. This provides a major challenge to the current blockbuster drug approach, because for large pharmaceutical companies, the way they conduct their business at the moment, they are interested inmarkets as large and as homogeneous as possible. A fragmentation into, for instance, a number of markets with each only $100 million would run counter to their main business strategy (Pisano 2002, p. 266).

As big pharmaceutical companies’ appreciation for genomics firms led to a speculative run on these firms, genomics, like the promises of many previous technological boom cycles, eventually became oversubscribed. In a capitalist society that considers the market as the preeminent instrument to disseminate new technologies, scientific potential has to lead to marketable and profitable outcomes sooner rather than later. Investors do not get involved for the beauty of science or the fascination of technologies, but for the financial metrics. In the case of genomics, big pharmaceutical companies and investors first lost a lot of money and then also their patience. There were neither a slew of new, genomics-based drugs, from which the old stewards of medicine would have profited. Nor was there a rebellious contender at hand – no Apple, no Google, no Napster - that would have allowed investors to profit from a new business model. On the contrary, if there was anything close to an

alternative business concept, it was the SNP consortium. Its purpose, however, was purely defensive as big pharmaceutical companies feared that the genomics start-ups would block that technological alley altogether. By the early 2000s, high tech companies' hopes based on the many possibilities created by the sheer mass of available data went up in smoke. Proclamations about the 'New Economy' were proven wrong and capitalism's creative destruction put things in order: Stock markets' speculative bubbles were purged of the many information-rich and cash-poor high-technology firms. The 'New Economy' lost and so did genomics. For the time being, old-style business persevered, among them Big Pharma[141].

7.7 Blockbuster Drugs: Innovations in Science and Marketing

In the long run, however, big pharmaceutical companies' unparalleled profitability has faced increasing criticism. To begin with, it has been questioned how innovative the current drug development process indeed is. For the period from 1998 through 2002, Angell (2004, pp. 54-5) found that of all the 415 drugs approved by the FDA to enter the U.S. market for the first time, only 14 percent were truly innovative[142]. In 2009 the ratio went up to 23 percent, which is hardly a proof that the drug development process has become more innovate[143].

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[141] Interestingly, Schumpeter has little to say about hyperbolic expectations from new technologies. His views on creative destruction and business cycles are based on companies that are driven out of business because the winners others adopted decisive technologies first, and not because most invested too much in the wrong technologies.

[142] Innovative drugs were both new molecular entities and were considered by the FDA to provide significant improvement over already approved products.

[143] As of July 2009, the FDA approved 35 new drugs, 8 were innovative new drugs as defined above. See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/default.htm; retrieved 7/29/09.

This figure is all the less impressive as the FDA's overall approval rate of new drug applications has risen simultaneously thanks in part to several industry-friendly policy changes that were described in chapter 5 (see 5.8). In sum, these data point to the scarcity of genuinely novel drugs and the relevance of 'me-too' drugs and the reapplication of already existing drugs for new medical indications.

Nonetheless, also non-innovative developments are costly. Pharmaceutical companies claim to spend on average about 10 to 14 percent of revenues on R&D. This figure is considerably lower than what biotechnology firms spend on R&D: Biotechnology companies included in this survey on average allocated 57 percent on R&D (see Table 4.5 Chapter 4). This difference is to be expected as biotechnology firms often times have no products but work as outsourced research departments for larger pharmaceutical companies. However, for both industries data about how much of the R&D goes into truly innovative medicines versus me-too drugs are hard to come by. The interviews with biotechnology executives in chapter 4 indicated that also small, allegedly high-tech focused biotechnology firms are often times engaged in copycat product research.

Therefore, irrespective of the involvement of biotechnology, the real costs of developing drugs have become a topic of debate. The figure most frequently quoted by industry representatives and politicians alike was produced by DiMasi et al., (2003), who calculated the expenditures to bring a drug to the market at $802 million. This estimate has been criticized for its methodology, because it relies on a non-random sample of firms and confidential data (Light and Warburton 2005 a; 2005 b). Equally indicative, however,

almost half of this figure is attributed to the costs of failed drugs and the opportunity costs of foregone, alternative investments. Seen this way, a pharmaceutical company is not in the business for developing drugs that have a positive effect on the public's health, but just another investment vehicle to optimize return on investment and shareholder value (Angell 2004, p. 45).

Despite the controversy about the DiMasi figure of $802million, there is consensus that drug development has become more lengthy and costly since the 1970s. Introducing a new innovative drug probably costs several hundred million dollars. But even the former CEO of Merck admits that the price for drugs is not determined by the costs for R&D. Instead, pharmaceuticals are priced according to

> *"their value in preventing and treating disease…it is the doctor, the patient, and those paying for our medicines who will determine its true value."* (Relman and Angell 2002, p. 32).

This is another way of saying, as one interviewed financial analyst did, that the cost for curing a particular ailment and therefore the potential of a market is *"what society is able to absorb"*[144]. In absence of an overarching regulatory entity for drug costs in the United States, marketing is the key intervening variable for shaping this absorption capacity. The absorption capacity of the American society for new and expensive drugs was considerably increased by a decision of the FDA in 1997, which allowed pharmaceutical companies to

[144] Interview 10/17/2008.

advertise their products directly to consumers. Since then, drug manufacturers' expenditures on advertising steadily increased up to $12 billion in 2006. Of this $4.8 billion were directly targeting customers, and $7.2 billion went into advertising for physicians. Over one decade, spending for consumer advertising had increased four-fold and that for the medical profession two-fold (Kaiser Family Foundation 2008, pp. 2-3). Yet direct-to-customer advertising does more than only promoting lucrative brands: It also transforms perceptions about health into diseases for which lucrative cures will be made available[145]. This business model became increasingly contested for many of the absurdities it created. For example, in 2000, direct-to-consumer advertising for the anti-arthritis drug Vioxx, whose lethal side effects on non-suitable prescribers later almost bankrupted Merck, cost the company $160.8 million in 2000 alone. This amount was more than what PepsiCo spent on advertising for Pepsi ($125 million) or what Anheuser Bush spent to Promote Budweiser ($146 million) (Ceccoli 2004, p.156).

By the mid of the 2000s, the public perception of large pharmaceutical companies was that of sophisticated marketing machines with limited in-house innovative capacity that profit from federally funded basic research[146]. For example, one study found that public research was at the basis of the five bestselling drugs in 2005 (National Institutes of Health 2000). Inevitably, the question was asked who picks up the tab for such a profitable and successful business.

[145] For instance, the drug company Lilly helped establish within the scientific community and at the FDA the clinical indication of women's premenstrual dysphoric disorder to market its anti-depressant Prozac for this new indication when Prozac's patent was about to expire in the late 1990s (Moynihan and Cassels 2005).
[146] See the first books on this issue by Angell (2004), Goozner (2004), Law (2006), and Moynihan and Cassels (2005).

Apparently, subsidizing the supply end of technology development for biotechnology and pharmaceutical companies – foreign and domestic – is not a contested issue. Direct funding for biomedical research, mostly through the annual NIH budget is globally unparalleled. Yet the NIH's $28.4 billion budget submitted for 2007 merely presented one percent of the United States' annual federal budget of $2.7 trillion. On the other hand, as a part of the general unease about rising healthcare costs, it has become increasingly contested that Americans pay considerably higher prices for prescription medicines than anyone else in the industrialized world. These elevated drug prices are an integral part of the competitive advantage of the innovation system of the United States. But as citizens increasingly have to pay this technology premium out of their own pocket, the question arises as to how long this important component of the United States biomedical innovation regime can – or should – be sustained.

The rise of prescription drug costs is an impediment to their broad availability. For instance, studies found that a lack of insurance coverage for prescription drugs made it more likely that nonelderly adults would not fill or use a prescription because of the cost (Kaiser Family Foundation 2008, p. 3). Another strategy of individuals without insurance to counter high drug costs was the import of drugs from Canada[147]. The relief from such purchases that amount to merely 0.3 percent of all U.S. prescription drug sales may be important on an individual level. Yet they did not provide much respite for society at large from rising drug costs, which, increasingly, also hurt individuals with health insurance.

[147] While 'Parallel Importing' of drugs is one of the most contentious issues among WTO member states, it was legalized on an individual basis in the United States in 2006 by Public Law 109-295.

Insurance plans reacted to prescription drug cost hikes by raising the copayments for drugs not included on a preferred drug list (ibid.). In particular, specialty drugs such as biologics push up the expenses for healthcare plans. Employers increasingly decide to include them only in their most expensive benefit plans, to which only a small population of employees has access (Elswick 2003). The consequences of both developments are the same: An increase in prices leads to increasing inequality in access to drugs.

At the end of 2008, triggered by the meltdown of financial markets and the onset of the deepest economic recession since the Great Depression, in the United States the issue of healthcare reform and cost control resurfaced. Even if it is rather unlikely that this will lead to a comprehensive overhaul of the United States healthcare system, the next section will draw some preliminary conclusions about the increasing cost awareness will affect the biotechnology industry's interests and therefore the functioning of the American innovation regime for biotechnology.

7.8 The (Not So) Great Transformation: Healthcare Reform in the 21st Century

Compared to circumstances that the Clinton White House faced in 1993, for the incoming administration of President Obama the environment for a comprehensive healthcare reform has changed in two important ways. First, healthcare has become a middle class problem. The topic has gained political traction not because of the many Americans, particularly children, being uninsured or underinsured, but because of working, tax-paying citizens who are no longer able to pay for medical care. Second, business acknowledges the competitive

disadvantage of the employment-based system. For instance, the former CEO of General Motors, Rick Wagoner, used to complain that his company spent more on health insurance than on steel, which put his company at a disadvantage with competitors such as Toyota, which benefits from Japan's universal health system[148].

As the most recent healthcare reform debate shaped up, the most encompassing healthcare overhaul, a national single-payer health insurance plan, remains out of reach. Such national approach, a 'Medicare for all', would have the potential to achieve universal coverage while at the same time curbing costs by eliminating duplicate bureaucratic structures and cut overheads (Woolhandler et al. 2003) . Yet as long as there is no broad-based social movement for this proposal, it is highly unlikely to be realized against entrenched, vested interests will most likely circumscribe the way in which alternatives are structured. So far, all proposals not only stop short of a single-payer plan, it remains also doubtful to what extent they will successfully alleviate the most contended issues of the current health system.

Hence, the discussion focuses on alternatives that are politically feasible while not necessarily effectively tackling the problems. The Democratic Party used its majority to pass on November 7, 2009, in the U.S. House of Representatives, the Affordable Health Care for America Act[149] and on December 24, 2009[150], in the U.S. Senate, the Patient Protection and Affordable Care Act.

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[148] See http://www.autoweek.com/article/20050401/FREE/504010702, retrieved 08/03/2009
[149] H.R. 3962.
[150] H.R. 3590.

At the beginning of 2010, passing a comprehensive health care reform has become increasingly difficult as the Democratic Party lost its filibuster-proof majority in the Senate when the Republican Scott Brown was elected to take over the seat of the late Edward Kennedy (D-MA). When President Obama announced his own proposal on February 22, 2010, which included ideas from both the Senate and House-passed bills, it was stripped down of many aspects addressed earlier on, such as new public health insurance option ('public option') as an alternative to private, for-profit health plans.

In contrast with previous health reform debates, health industry interest groups have abstained from head-on resistance. For example, in May 2009 during a highly publicized meeting with President Obama, health industry leaders, including representatives from the American Health Insurance Plans and PhRMA, promised to collaborate with the administrations efforts to overhaul healthcare and to decrease the United States' healthcare spending by 1.5 percent annually. The first stakeholder to come up with a concrete concession was PhRMA, which in June 2009 declared to forego $80 billion in drug sales to seniors and federal health programs over the next decade. Some $36 billion would come from lowering drug prices for Medicare recipients who fall into the 'doughnut hole' of coverage under Medicare's prescription drug plan. This concession may have been more a preemptive move than a real economic sacrifice: Data for 2009 indicate that wholesale drug prices continued their ascent by more than 9 percent, adding another $10 billion to the revenues of pharmaceutical companies and the United States' drug expenditures. Consequently, the industry has been pressured since to deliver further cost cuts (Wilson 2009) and both the House and the Congress' healthcare bill as well as President Obama's

proposal in February 2010 urge pharmaceutical companies to accept bigger discounts to close the donut hole[151]. At the same time, one of the collaterals of this struggle was Billy Tauzin, Phrma's CEO, who resigned in February 2010 after having been criticized by pharmaceutical firms for making too far-reaching concessions to accept healthcare reform too early (Kirkpatrick and Wilson 2010). In sum, therefore, whereas comprehensive healthcare reform is nowhere in sight, the issue of cost cutting in healthcare, including for prescription drugs, will most likely persevere.

Also the biotechnology industry seems to realize that the current climate makes cost cuts inevitable. Throughout the Medicare reform debate of 2003, the biotechnology interest group BIO continued to warn that *"small biotech companies could fail under even the threat of price controls"* (2009). Similarly, the investment community continued to warn about the specter of price controls in the U.S. prescription drug market:

> *"The top threat facing the* [biotechnology, V.L.] *industry is the escalation of price controls and access regimes. In particular, the specter of price controls in the U.S. market would make it difficult to continue to fund the industry's innovation."* (Ernst & Young 2008, p. 5)

But as some kind of healthcare overhaul seems to become more likely than not, the more enlightened biotechnology actors, such as the CEO of Exelixis, a San Francisco biotechnology company, acknowledge that

[151] See http://www.whitehouse.gov/sites/default/files/summary-presidents-proposal.pdf (retrieved 2/28/10).

> *"some type of price pressure on drugs is likely to be part of the reform. The way in which those pressures become institutionalized will have important consequences for the biotech industry…it will be important to work with legislators to achieve an outcome that is reasonable for our industry and responsive to the needs of society."* (Scangos 2009, p. 424)

This is not to say that the industry should be expected to give away too much too freely. For instance, as expenditures on biologics as the fastest growing segment of pharmaceuticals have become increasingly scrutinized, legislation to set boundaries to the exclusive commercial rights on generic versions of biologics, so-called 'follow-on biologics' has become a contested issue. First draft bills were granting only a limited period of exclusive rights – 5 years – to the makers of original biologics. But thanks to the well-functioning political machinery of interest representation, BIO managed to extend this to 12 years in recent draft legislation (Greenwood 2009), proving again the industry's leverage to influence policy-making process[152].

Yet most consequential for the future of the drug innovation regime may in fact be that the American Recovery and Reinvestment Act of 2009 allocated $1.1 billion to research carried out by federal agencies on comparative effectiveness of treatments and drugs already on the market[153]. Such comparative effectiveness studies are heavily opposed by

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[152] The 12-year provision is also included in President Obama's own proposal from February 2010 (Kaiser Family Foundation 2010, p. 25).

[153] As the global economic downturn lowered investors' willingness to bankroll biotech companies' losses any further, BIO let loose of market-only principles that they so eloquently made during the Medicare reform

biotechnology and pharmaceutical alike. They argue that it would inevitably lead to a centralized government agency like the UK's National Institute for Health and Clinical Excellence (NICE). Industry representatives argue that a government-run entity assessing efficiency would rationalize access to technology if such studies were a prerequisite for obtaining regulatory approval or healthcare coverage. In any event, federally administered comparative studies would potentially change the dynamics between doctors, patients, and pharmaceutical companies. Unlike comparative effectiveness studies that are carried out by CROs for the sake of marketing or other undisclosed reasons, the implementation of the bill could lead to scientific comparisons that would make drug efficiency susceptible to public scrutiny. This would undermine an important pillar of the current innovation regime, because it would become harder for companies to launch 'me-too drugs' that currently hold a considerable share of newly approved drugs in the United States.

While the current healthcare struggle will certainly have important consequences for the innovation model pursued by biotechnology and pharmaceutical companies, these industries may not be the decisive corporate actors that decide the destiny of healthcare reform. In the history of the United States, the longest-lasting track record of derailing national solutions for healthcare is held by the medical profession and insurance companies. Without them, it seems, no reform can be achieved, but with them the meaning of reform may get lost in the process. It also proves that healthcare is more deeply rooted in national politics, histories, and gospels about commonly held values, than many other

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debate of 2003. Instead, the trade group lobbied cap-in-hand to have some of the $787 billion economic stimulus package directly injected into the biotechnology industry (Fox 2009). These efforts failed and ongoing economic insecurities will inflict more creative destruction on the industry.

issues of public policy. This was a lesson that in her time also the icon of neoliberal deregulation, Margaret Thatcher, had to learn. Thatcher, for whom there was no such thing as society, and suspicious of all forms of common burden-sharing, failed miserably when touching the British National Health Service (NHS). She initially had hoped to establish a mandatory private health insurance system. However, this privatized alternative was too costly and was confronted with the popularity of the all-inclusive, free-of-charge NHS, so that privatization plans were quickly given up (Pierson 1994, pp. 132-34). Ideological sea-changes create windows of opportunity for real, historical, political change. They hardly ever remake institutions from scratch.

7.9 Biotechnology After the Failure of Neoliberal Economics

This political economy of the medical biotechnology industry analyzed the neoliberal political conditions under which biotechnologies have been invented and commercialized in the United States. Neoliberalism assumes that the individual desire for profit is the most productive engine for innovation, from which society will receive broad benefits as a whole. While there is no doubt that private profits often also increase the wellbeing and wealth of the general public, the question remains what to do when market incentives are not sufficient to spark innovation. The answer to this question is all the more pertinent when it comes to contemporary global health challenges. It is one of the unavoidable, unintended consequences of the increase in global exchange of goods and people that it also increases the global dissemination of new health hazards.

New types of viruses, including HIV, and pandemics as swine and bird flu pose new threats against which individualized protection becomes increasingly impossible, even for the upper echelons of the global pyramid of wealth and health. Solutions can only take place at a global level. Biotechnologies may be part of it, but only if they were embedded in a broader strategy towards health as a global public good. For the time being, however, most biotechnologies are devised to be a profitable individual commodified quick technological fix, out of reach for the majority of the globe's population.

As these demands for global health solutions are currently neglected, the flipside of the same coin is that the demand side for biotechnologies is shaped by the most lucrative market. America's healthcare market and its unparalleled profitability are the result of a long history of healthcare politics that have always had a neoliberal streak in that it put private actors in the driver's seat for the provision of a public service. Ultimately, the neoliberal prescriptions that structured creative destruction in the biotechnology and pharmaceutical industry had several conflicting effects. On the one hand, the United States became the country in which the largest and most competitive biotechnology industry developed. On the other hand, the products that this supply-side driven innovation regime generated have exacerbated the tension in America's healthcare, which is too expensive and too exclusionary.

Arguing that the public is served best by private entrepreneurship leaves decisions about resource allocations completely to the market. Yet this ideological proposal led to the current legitimacy crisis of neoliberalism. It is best exemplified by calculations for

biomedical innovation based on ‘opportunity costs’. By putting the costs of foregone investments at the center of high R&D expenditures and, ultimately, America’s exceptionally high drug prices, the entrepreneur will be remunerated for what he does with his money, but also for what he does not do with it. Laissez-faire prescriptions should encourage the free choice of investment opportunities. If investors decide that resource allocations elsewhere are more profitable than products for human health, so be it. Consequently, healthcare sees itself in a heads-on competition with other productive assets or purely speculative financial vehicles. Future studies will probably elucidate the extent to which the finance-driven economic boom of the mid 2000s first attracted, and then destroyed, resources that otherwise would have been invested in health products and services. In any event, putting increasing returns on investment into the drivers’ seat for fulfilling society’s health needs inevitably leads to a collision, because health is a Polanyian fictitious commodity. As an unintended side effect of speculative energy and the commodification of health, healthcare in the United States has finally turned into the political crisis that it deserved to be for long. Healthcare inequalities have generated social and political tension that are the driving motor for current health reform efforts. The outcome will be far from comprehensive, but it will certainly lead to greater cost awareness and an increasing role for the state. Therefore, the institutionalization of the political compromise will affect to a large extent how biotechnologies will be invented and commercialized in the future.

Appendix

Summary company description

Interview Date

Enterprise (Address)
Name Interviewee

0. Interviewee Information
0.1. What is your current responsibility within this company?
0.2. Where have you been working before?
0.3. How did you become engaged with this company?

1. General Company Information
1.1. When was the enterprise founded?
1.2. How was the enterprise founded?
- wholly new organization
- new subsidiary of an existing organization
- spin-off organization (e.g. from university)
- joint venture of two or more existing organizations
- privatisation
- other

1.3. How is the enterprise currently owned?
1.4. How was the enterprise originally capitalised?
- Private Investment
- Public Funding
- Other Sources

1.5. How much capital is currently needed and how is it generated?
- Re-investment of profits
- Private investment
- Public Funding
- Other Sources

1.6. Number of employees (absolute figures or percent)
- Management
- Administration
- R&D
- Production
- Sales Department
- Others

1.7. How has employment grown in your enterprise?
1.8. How have revenues of your enterprise developed? (absolute or %)
1980 - 1989
1990 - 1994
1994 – 1999
2000 – current

1.9. What are the main products respectively lines of products manufactured in your enterprise?
- Product lines / Group of Products

2. Employment and Qualification

2.1. What are the main types of qualification your employees possess? (PhD, Masters, BSc, Highschool)
- PhD
- Masters
- Bachelor
- Highschool/None

2.2. Which labour markets do you look to or the recruitment of new personal?
- Own enterprise
- Regional
- National
- International

2.3. If colleagues leave your enterprise, to what jobs or other organisations would they normally go?

3. Co-operation

3.1. - 3.3. With which enterprises, research institutes or other organisations do you co-operate in production, distribution/marketing, or R&D?

3.4. What is the quality of relations/co-operations you maintain with important large enterprises?

3.5. Of those organisations mentioned above which are the most important for future development?

4. R&D, Production and Distribution

4.1. If your company faces a significant technological challenge, who do you approach for technical collaboration and why?

4.2. With which enterprises/research institutes would you like to co-operate in the future and why?

4.3. How is technological development financed?
- Revenues:
- Private Funds: Bank loans
  Venture capital
- Public Funds: National level
  Regional level
  Local level (city or municipality)
- Other (e.g. stock market)

4.4. How much money has been spent on R&D in the last decade?
Total:
- Own research units
- universities/research units

4.5. Which regions or countries do you envision as new markets?
4.6. What kind of measures do you take to open up new markets?

5. Assistance Programs
5.1. What public support programs available for your business are you aware of?
5.2. What kind of financial support or public assistance programs have you been using to date?
- state (government) programs
- national (government) programs
5.3. What support programs do you intend to use in the near future?
5.4. How would you judge the relevance of public assistance programs?
- state (government) programs
- national (government) programs

6. Conclusion
Could you briefly sum up the main reasons for the location of your company?

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