THE NATURE OF CAPITAL IN THE KNOWLEDGE-BASED ECONOMY: THE CASE OF THE GLOBAL PHARMACEUTICAL INDUSTRY

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ABSTRACT

By distinguishing the pharmaceutical industry (producing wealth) and the pharmaceutical business (capitalizing income), this dissertation explains why the increasing earning capacity in the global pharmaceutical business is paralleled with a decline in therapeutic innovation. It contends that increasing profits is found not in a surge of productivity but, instead, in the capacity by dominant pharmaceutical firms to increase their control over the medical knowledge structure. The knowledge-based economy, in the case of pharmaceuticals, should not be interpreted as an accumulation regime based on intellectual capital and permanent innovation but, instead, as an accumulation regime based on institutional transformations that bestow greater corporate power to dominant firms over the industry and the community in general. The capitalization of knowledge, that is the increasing differential earning-capacity for knowledge-based firms, is possible because of new institutional settings that were put in place to increase dominant firms' monopolistic power since the beginning of the 1980s. As such, the link binding knowledge, productivity and profitability is broken and we observe rather a link between the knowledge structure, power accumulation and profitability.

To Manu,

My little seed of hope.

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LIST OF ABBREVIATIONS

ACTPN :	Advisory Committee on Trade and Policy Negotiations
ANBERD :	Analytical Business Enterprise Research and Development database
ANDA :	Abbreviated New Drug Application
AHP :	American Home Products
ATC :	Anatomical Therapeutic Chemical
BERD:	Business Enterprise Research and Development
BMS:	Bristol Myers Squibb
CAFC:	Court of Appeals for the Federal Circuit
CEO :	Chief Executive Officer
CGPA :	Canadian Generic Pharmaceutical Association
CIA :	Central Intelligence Agency
CME:	Continuing Medical Education
CMO:	Contract Manufacturing Organization
CNAM:	Caisse National de l'Assurance-Maladie
CPI:	Center for Public Integrity
CPTECH:	Consumer Project on Technology
CR_4 :	Concentration Ratio for the 4 largest firms
CRO:	Contract Research Organization
CTIETI:	Committee on Technology and International Economic and Trade Issues
DNA:	Deoxyribonucleic acid
DTCA :	Direct-to-Consumers Advertising
EFPIA :	European Federation of Pharmaceutical Industries and Associations
FDI:	Foreign Direct Investment
FTC :	Federal Trade Commission
GATT:	General Agreement on Tariffs and Trade
GDP :	Gross Domestic Product
GFCF:	Gross Fixed Capital Formation
GPB :	Global Pharmaceutical Business
GPIA:	Generic Pharmaceutical Industry Association
HAI :	Health Action International
HMO :	Health Maintenance Organization
IFPMA :	International Federation of Pharmaceutical Manufacturers Associations
IMS :	Intercontinental Marketing Services
IND :	Investigational New Drug
IP :	Intellectual Property
IPC:	Intellectual Property Committee
IPE:	International Political Economy
IPR :	Intellectual Property Right
IRR:	Internal Rate of Return
J&J :	Johnson & Johnson
KBE :	Knowledge-Based Economy
KOL:	Key Opinion Leaders

LDC:	Low Developed Country
M&A :	Merger and Acquisition
MAT:	Moving Annual Total
Mfg :	Manufacturing
NAICS :	North American Industrial Classification System
NBE:	New Biological Entity
NBF:	New Biotechnology Firm
NCE:	New Chemical Entity
NDA :	New Drug Application
NIHCM :	National Institute for Health Care Management
NME:	New Molecular Entity
NPV:	Net Present Value
OECD :	Organization for Economic Cooperation and Development
OTA:	Office of Technology Assessment
OTC :	Over-the-Counter
P&G :	Procter and Gamble
PICTF:	Pharmaceutical Industry Competitiveness Task Force
PhRMA:	Pharmaceutical Research and Manufacturers of America
PMA:	Pharmaceutical Manufacturers Association
PMDD:	Premenstrual Dysphoric Disorder
PMPRB :	Patented Medicines Prices Review Board
RAMQ :	Régie d'Assurance-Maladie du Québec
RCTs :	Randomized Clinical Trials
R&D :	Research and Development
ROA:	Return On Assets
ROE:	Return On Equity
ROI:	Return On Investment
ROR:	Return On Revenues
R_X :	Medical Prescription
R_X&D :	Canada's Research-Based Pharmaceutical Companies
TRIPs :	Trade-Related Aspects of Intellectual Property Rights
TNC:	Trans-National Corporation
UN:	United Nations
UNICE:	European Union of Industrial Employers' Confederation
UNIDO :	United Nations Industrial Development Organization
USPTO:	United States Patent and Trademark Office
USTR:	United States Trade Representative
VFA :	Verband Forschender Arzneimittelhersteller
WHO :	World Health Organization
WIPO:	World Intellectual Property Organization
WTO :	World Trade Organization

"The hegemony of neoliberal policies has little to do with self-regulating markets, supply and demand, or even the "economic" as an autonomous category. Neoliberalism is not the *Wealth of Nations* 2.0; nor is it latter-day Cobdenism, healing the world's wounds through peaceful free trade; and, most certainly, it isn't the advent of the stateless market utopia romanticized by Friedrich von Hayek and Robert Nozick. On the contrary, what has characterized the long boom since 1991 (or 1981, if you prefer) has been the massive, naked application of state power to raise the rate of profit for crony groups, billionaire gangsters, and the rich in general. [...] It has been corrupt insider political power, nothing less, that has given away the global commons to a plunderbund"

— Mike Davis and Daniel Bertrand Monk, *Evil Paradises*

1. INTRODUCTION: THE NATURE OF CAPITAL IN THE KNOWLEDGE-BASED ECONOMY

The 21st century is auguring a world where production has shifted literally from 'hardware' to 'software', or so it is claimed. This "New Economy", or knowledge-based economy, is the radical transformation of industrial societies into information societies. Knowledge, it is claimed, constitutes the main competitive advantage for every nation, and the accumulation of such knowledge is becoming the new form of capital making up the core of capitalist competition. Knowledge is said to have replaced labor in the creation of value. In the knowledge-based economy (KBE), technological change is seen as the principal force driving enhanced economic growth. Increasing production and diffusion of information and communication technologies in the 1980s, many assert, has developed human capital and enhanced innovation and entrepreneurship, such that, together with a favorable business environment, they have transformed the nature of capital and economic growth (OECD 2001a; APEC 2000; Economic Report of the President 2006). Many argue that industrial capitalism, in which capital accumulation was based on tangible means of production (capital goods), is being replaced by a new, immaterial, economy, in which knowledge, information and intelligence have become the new form of capital, held as firms' main assets and principal source of wealth. Capital goods are becoming immaterial and "the factors that have become most important to economic growth and societal wealth are 'intangible', or 'nonphysical'" (Blair & Wallman 2001), and the economy is becoming "weightless" (Quah 1997: 55).

A New Accumulation Regime?

The U.S. Economic Report of the President 2006 (2006, 218) estimates that approximately 70% of the value of American publicly traded companies comes from intangible assets, whether protected by intellectual property rights or not. An important new literature hails this "New Economy", because the increasing business research and development (R&D) expenditures create an economic regime of permanent innovation that increases both productivity and employment while assuring a high rate of profit for investors[1]. While some consider the "New Economy" to be mainly a global merger wave (Bichler and Nitzan 2002a) or an ideological discourse feeding on a speculative hubris that ended with the crash in 2000 (Henwood 2003), most assert that the socio-economic transformations occurring with this emphasis on the capitalization of knowledge signal the dawn of a new regime of capital accumulation based on incessant innovation.

This optimistic discourse legitimizes neoliberal policies by promising a general increase for the social welfare due to a new "accumulation regime"[2] based on the production and diffusion of knowledge. According to this discourse, the diffusion of technology and knowledge increases labor productivity (and total factor productivity), which diminishes costs of production and consequently inflation. This "new growth" increases the level of qualified employment and enhances stock market performances. All this contributes to the improvement of general welfare, which increases demand for services and thus the level of

[1] See for example: Castells (2000); Economic Report of The President (2001; 2006), Innovation in Canada (2007), Greenspan (1998; 2000), OECD (1999; 2001a; 2003).

[2] According to Robert Boyer (1986, 46), an "accumulation regime" can be defined as "the whole of regularities securing a general and coherent progress in the accumulation of capital, that is by bringing down or by spreading in time distortions and imbalances emerging from the process itself" (author's translation).

employment. With proper incentives for innovation by increasing profits for investments in R&D, it is argued that economies can achieve durable growth through a strong effective demand that is not inflationary. Innovation, as the constant creator of new markets at the expense of old ones (the Schumpeterian creative destruction process being at work), creates constantly new opportunities for investment with strong returns on capital. While this new accumulation regime can seem enduring to some analysts, its nature and the reasons for its endurance must not be taken for granted. Critical political economy must not only observe the actual transformations of the capitalist system, but also question the reasons and causes of those transformations, and their impact on the social and economic order. The information society remains a capitalist society, and the involved social restructuring that goes with it benefits some more than others.

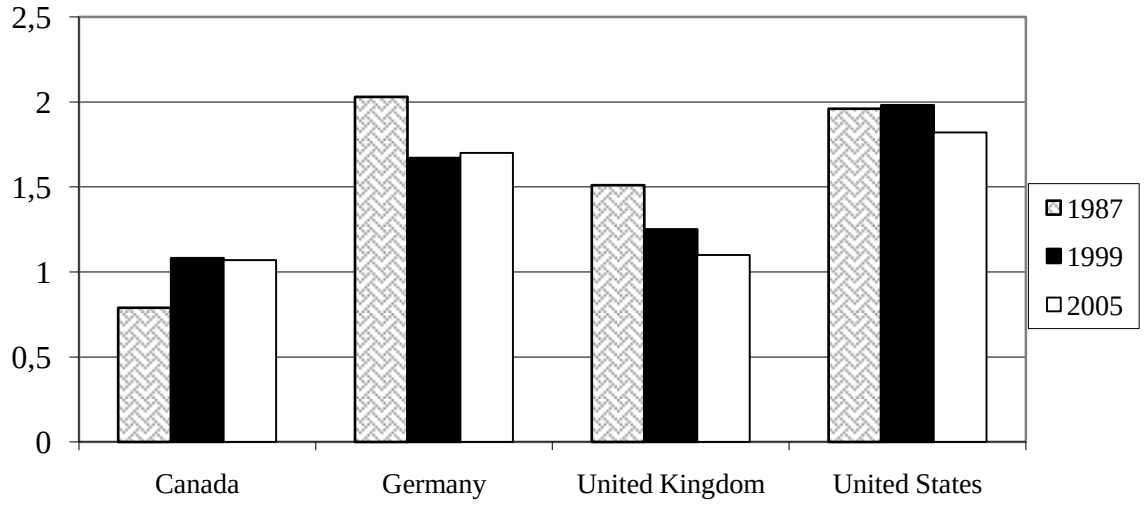
What is "New", in the New Economy?

The main question for this dissertation is the understanding of how the "new" capitalist economy is different from the "old" one? If one answers that knowledge and intelligence now play an important role in the economy because they are a new form of capital, then it means that they did not previously play that role. Are political economists only beginning to understand the economic dimension of knowledge and the cognitive dimension of the economy? Even before analyzing the discourses that feed the idea of the emergence of a KBE, is it really possible to claim that knowledge is only now becoming the focus of accumulation? For example, the idea of a knowledge-based economy implies that firms are now spending much more on R&D, since their innovation capacity has become their main competitive asset. One should, thus, expect a steep increase in R&D investments during the

1990s, throughout which the discourse about the KBE emerged. Data on R&D in developed countries, however, shows a different story. Since 1987, the Organization for Economic Cooperation and Development (OECD) has computed private R&D expenditures for its member states.[3] By comparing R&D spending by business enterprise as a share of GDP, most developed countries associated with the "New Economy" discourse show, in fact, a substantial decrease in R&D spending, Canada being the exception (Figure 1.1).

Figure 1.1: Business Enterprise Research and Development as a share of GDP

(in different OECD countries in 1987, 1999 and 2005; %)



Sources: OECD Science, Technology and Industry Scoreboard 2007; ANBERD Database.

[3] Some data go back to 1977 but it uses a different mode of computation and makes impossible valid historical comparisons. The method has been corrected and refined since 1987 with the Analytical Business Enterprise Research and Development database (ANBERD).

Discourses describing the KBE do not match the numbers. They do, however, insist on the strategic importance of firms investing massively in knowledge production (or R&D), in order to develop and maintain their competitive edge in the global economy. In reality, most R&D expenditures for basic research (as compared to product development) still come from public funds. For example, in the case of global basic research for health sciences, public money accounts for 84.2% of all expenditures (Light 2006, 35). New questions arise: who finances knowledge production, who produces it and who benefits from it? Taking for granted that knowledge-based enterprises are the answer to all those questions is surely misleading. Instead, appreciating the novelty in the KBE demands understanding the restructuring of social power associated with it.

The first issue is to identify whether or not we are entering a new phase of capitalism, in which the immaterial dimensions are transforming the logic and nerve centers of capital accumulation. It is reasonable to suggest that this is indeed the case, given the various institutional transformations that brought about both a race for patents and an important profit surge for dominant knowledge-based firms. The capitalization of knowledge is not necessarily new, but the institutional forms of this capitalization since 1980 are, because they increase the earning-capacity of some agents to the detriment of others. Another important issue, however, is to consider whether such socio-economic transformations are the necessary results of technological progress, as advocates of the KBE often argue, or whether the KBE is the result of planned socio-institutional transformations for the benefit of vested interests. In a nutshell, is technological progress transforming the face of capitalism, or are capitalist institutions transforming the face of knowledge, by implementing institutions that

allow greater private control over the commons of public knowledge? This dissertation weighs in decisively in favor of the latter argument.

The task of understanding the nature of socio-economic transformations is pressing, but prevailing discourses about the "New economy" contain serious shortcomings insofar as they are ahistorical, positivist and imply a non-conflicting conception of science and technology. The latter tends to ignore social, political or cultural contradictions brought forth by the capitalization of knowledge. These approaches, apparent in the OECD literature (2001a; 2003), evade the fact that "knowledge structures" are embedded in capitalist institutions in a way that serves vested interests, by restraining production and stifling capacities to create greater wealth for the public good within an innovating economy. An institutionalist approach, emphasizing the capitalist dimension of the KBE and analyzing empirically the ways in which capitalist entities capitalize knowledge, surely renders a firmer grasp on the nature of contemporary transformations in the capitalist economy.

Capitalizing Knowledge: Production or Power

The main problem undermining analyses of current transformations in the economy is the hazy conceptualization of knowledge and capital to date. First, almost all economic models have failed to integrate the cognitive dimension of the economy, since standard models consider knowledge structures to be exogenous, forcing economists to understand a KBE as radically new. Second, in the main economic paradigms (be they post-Keynesian, neo-institutionalist or neoclassical), capital has been normally understood in terms of means of production and measured in terms of productivity. The capitalization of knowledge is thus analyzed by reducing knowledge to a simple factor of production that can be bought and sold

like any other commodity. This failure to grasp the complexity of the cognitive dimension of the economy, and the preconception that any capital, as a source of profitability, has to be measured in terms of productivity, impede a clear understanding of actual socio-economic transformations. It nourishes the belief that higher profits in the "New Economy" must be the result of greater innovation and productivity.

Following the Marxist approach that analyzed capital in terms of social power, an alternative approach to analyze capital accumulation was first proposed by Thorstein Veblen (1904) and later developed by Shimshon Bichler and Jonathan Nitzan (2002b; 2004; 2009). This alternative approach considers that capital is not measured by its productivity, but, instead, by its social power or its capacity to control technology and the community in general. It emphasizes the institutional evolution of power structures underlying economic transformations, and thus offers a new understanding of the KBE in terms of evolving social power, leaving aside the *a priori* postulate of increased productivity. Similarly, the approach adopted here suggests that the novelty in the KBE does not rest on new forms of productivity but, instead, on new institutional means for private control over technology, economic production, and society at large. The question is, thus, to understand the nature of the institutional evolution and how it impinges on the dynamics of capital accumulation in the KBE.

The Case of the Global Pharmaceutical Business

Understanding institutional evolution of the overall power structures associated with all technological sectors is not an easy thing. Just as Karl Marx observed the workings of industrial capitalism, describing in detail the organization of labor and calculating the

progression of work hours in factories, it is also absolutely necessary to examine the workings of the KBE before assessing about its nature. Analyzing the evolution of power structures can be tricky if one tries to analyze many different sectors, each with its own specific logic. This dissertation is surely not of the same magnitude as Marx's *Capital*, and will focus its observations on a specific sector of the KBE: the global pharmaceutical business (GPB). The examination of the GPB allows for a detailed analysis and in-depth understanding of a critical sector in the contemporary capitalist economy. By choosing to focus on one sector, it is probable that no general conclusion concerning the capitalist economy as a whole can emerge from this dissertation. However, for what may be lost in terms of analytical breadth, the dissertation offers important gains in terms of depth of understanding and critique of actual capitalist dynamics at work.

The global pharmaceutical business is particularly fit to illustrate the point that the KBE should be understood as the emergence of new institutional mechanisms for private control over technology and society at large. At least four reasons support this point. First, prevailing discourses about this sector are intimately linked to a vision of actual transformations of economies and societies. The pharmaceutical business is seen as one of the driving forces of the emerging "New Economy," in which capitalization of knowledge becomes the locus of production and profits. Curiously, however, the increasing differential profits in the last 20 years of this business in comparison to all industries (Chapter 2), has been paralleled by a growing *drought* in pharmaceutical innovation (Pignarre 2003; Le Fanu 1999; Economist 2004; Berenson 2006). Second, the pharmaceutical sector is one of the most heavily regulated by public authorities, and thus debates concerning this business are always partly political, and must be tackled not only from an industrial or economic point of view,

but also using a political and social perspective. Third, the pharmaceutical industry has always been a knowledge-based industry. It is, therefore, difficult to explain pharmaceutical firms' rising profits simply by contending that knowledge has now become a new source of productivity. Historically, the appropriation of knowledge has been a source of control over the technological community by creating important barriers to entry. The capitalization of knowledge through patents allowed the global pharmaceutical business to take the form of a cartel as early as the 1920s. Finally, an ultimate reason for the relevance of studying specifically the pharmaceutical sector is the importance of dominant pharmaceutical firms, and especially Pfizer, as the driving force of institutional transformations in the 1980s. Dominant pharmaceutical firms, especially American ones, were critical in reshaping the knowledge structure, by extending commodification of knowledge and intellectual property rights (IPR), so as to maintain their dominant position in the industry and rebuild America's technological dominance over the world economy.

The case of pharmaceuticals will be used as the guiding light to understand the *why* and the *how* of capitalist transformation, which has both given rise to the discourse about the KBE and been associated to an increasing profitability of knowledge-based firms since the 1980s. By historically contextualizing institutional transformations that have affected earning capacity in the GPB since 1980, this dissertation argues that *the knowledge-based economy, in the case of pharmaceuticals, should not be interpreted as an accumulation regime based on intellectual capital and permanent innovation but, instead, as an accumulation regime based on institutional transformations that bestow greater corporate power to dominant firms over the medical knowledge structure and global technological capacities.* By understanding the institutional evolution of power structures that parallel growth in profits,

the dissertation not only refutes standard approaches that explain rising profits in terms of a surge in innovation and productivity, but also provides an extensive critical understanding of the dynamics of corporate power in a specific industry, setting the agenda for effective reforms.

The Argument

Did knowledge became a new form of capital, and how can firms capitalize knowledge as a source of earning-capacity? Does the profitability entailed by the capitalization of knowledge mean greater productivity and serviceability to the community? In the case of the pharmaceuticals, what are the institutional transformations that made possible the surge in differential profits? To answer these questions, it is necessary to provide a theoretical foundation about the nature of capital and its relationship to knowledge. Chapter 2 introduces the analytical framework of this dissertation. After identifying the shortcomings of standard approaches to knowledge capitalization, the chapter introduces an institutionalist perspective with a power theory of capital based on the works of Thorstein Veblen, Shimshon Bichler and Jonathan Nitzan. The power theory of capital allows a quantitative analysis of the emergence of the KBE in the pharmaceutical sector in terms of differential profits. By comparing the differential evolution of profits in the pharmaceutical sector as compared to other sectors, such quantitative analysis offers solid ground to interpret qualitatively the reasons behind growing differential profits.

Chapter 3 focuses on the GPB and shows how increased earning-capacity since 1980 is linked to an important decline in therapeutic innovation. After exploring the sector in terms of sales, production and segmentation, it evaluates claims offered by the industry that its high

prices for products reflect increasing costs of R&D. Finally, it assesses, both quantitatively and qualitatively, the decline of innovation and productivity in this sector. Thus, the chapter demonstrates that rising profits in pharmaceuticals associated with the emergence of the KBE has nothing to do with a surge in productivity and innovation.

Institutional evolution is a historical process, and the understanding of institutional transformations in the pharmaceutical sector requires historicizing the GPB. Chapter 4 relates the history of the pharmaceutical sector from its origins in dominant German firms prior the First World War. By focusing on the role of cartels and patents in the institutional organization of this sector, the chapter explains how American firms came to dominate the GPB, with the emergence of the American-made business model of the 1950s that combined a therapeutic and marketing revolution. The business model, however, evolved in the 1960s and 1970s due to the exhaustion of the therapeutic revolution, as well as the routine implementation of systematic randomized clinical trials (RCTs). The chapter concludes by assessing the (perceived) decline of the American Pharmaceutical Business at the end of the 1970s on two grounds: 1) the revival of generics and 2) a globalization process from which emerged important international competitors. These perceived challenges to American dominance are the necessary starting points for understanding the institutional reactions that rendered transformations in the power structures of the GPB in the 1980s. Ultimately, this would give rise to what analysts now call the knowledge-based economy.

Chapters 5, 6 and 7, focus on dominant American pharmaceutical firms and develop the core of the argument of this dissertation, by explaining in detail the institutional reasons behind their increasing profitability in spite of declining innovation. The chapters analyze the differential evolution of firm size (breadth) and the differential evolution of their profit rate

(depth). The detailed quantitative analysis of differential evolution of profitability for pharmaceutical firms — compared against other sectors — is used as a vehicle to understand the qualitative institutional transformations that effect increased earning-capacity, which is casually associated with the emergence of the KBE. Chapter 5 focuses on the breadth of pharmaceutical firms, and shows that dominant firms are growing in size at a faster pace than those in other sectors. It demonstrates that most investment in new productive capacities was made by smaller pharmaceutical firms (especially in biotech) in cooperation with universities. Dominant firms, in better control of commercial networks of distribution, normally avoided risky innovation by concentrating on buying back smaller firms if their new compounds looked commercially promising. This new division of labor in pharmaceutical innovation between dominant firms and a supporting nexus has been central to the emergence of the KBE. It has allowed dominant firms to externalize risky R&D investments while still appropriating the commercial benefits of innovation. Such restructuring was made possible only because of the important relaxation of antitrust policies undertaken by the Reagan Administration, which allowed greater mergers, acquisitions and cooperation between dominant firms, in order for the United States to gain back its lost market shares in the global arena.

The accelerating size (or breadth) of dominant pharmaceutical is not the only reason for its growing profits, because profit rate (depth) also increased sharply in comparison with other sectors. Chapter 6 discusses the institutional reconfigurations that occasioned increasing profit rates in pharmaceuticals and focuses on the greater monopolistic power obtained by dominant firms. These actors increased their monopolistic capacities through mergers and acquisitions but also due to a restructuring of the intellectual property regime

that favored dominant firms in knowledge-based sectors. After analyzing the evolution of corporate concentration since 1980, the chapter argues that transformation in the patent system were central to anything akin to a KBE since it greatly increased corporate and legal control over technology, production and the community at large. The chapter analyzes institutionalization of new rules in intellectual property rights both in the U.S. and globally — and shows how their contribution to increased profits via restraint on innovation.

Chapter 7 focuses on a crucial dimension of the increasing depth of the GPB: promotion. The chapter analyzes the evolution of the cost structure in the GPB, in order to show how central promotion, as compared to R&D, has become for dominant pharmaceutical firms. Promotion is the main lever for dominant pharmaceutical firms to influence every aspect of the medical profession, advancing costly new products even when their effects on patient welfare are sometimes dubious. Increasing profit alongside declining innovation was made possible only because pharmaceutical firms tightened their grip on prescribing habits among physicians, encouraging an inclination towards more expensive products with ever less therapeutic benefit. As long as aggressive promotion props up low innovation, the current business model can be maintained as a commercial success.

The final chapter sums up the whole argument, identifying the main components of the business model in the pharmaceutical sector since 1980. Revisiting the question about the nature of capital in the knowledge-based economy, the chapter synthesizes the case of the pharmaceutical sector, in order to problematize the routine association between capital/profits and productivity/innovation. Summing up the results of the case study, it assesses how a KBE was enabled through new institutional settings, allowing greater corporate control and power over socio-technological capacities. Moreover, it suggests that

the link between knowledge, productivity and profitability cannot be assumed, and that political economy should consider more seriously the link between knowledge structure, power accumulation and profitability. While the argument remains reformist rather than revolutionary, it is based on a radical questioning of the presumptions and received ideas that prevail in the commonplace and academic discourses about economics and the economy in general.

2. CAPITAL, KNOWLEDGE AND POWER IN PHARMACEUTICALS: AN INSTITUTIONALIST PERSPECTIVE

"The outcome of any serious research can only be to make
two questions grow where only one grew before"
- Thorstein Veblen

Many theoretical analyses aim at interpreting recent transformations in capitalist economies, in which knowledge is considered to become central for growth and competitiveness. To say the least, there is no consensus about how to interpret those transformations. The main limits to standard approaches are their preconception that capital must in some way be defined in terms of productivity. For example, if profits are growing for pharmaceutical firms, then it "has to be" because they are becoming more productive and innovative. In the case of pharmaceuticals, growing profits combined with decreasing productivity thus seem contradictory. This chapter first makes explicit the productivity doctrine of capital in standard economics and explains why it is necessary to get out of this doctrinaire preconception and to focus, instead, on the social structures in which the production and diffusion of knowledge are embedded. Second, in order to develop an analysis in terms of power within the social structures, the foundations of an institutionalist perspective will be introduced. Third, the chapter will introduce an institutionalist power theory of capital, based on the works of Thorstein Veblen, Shimshon Bichler and Jonathan Nitzan, and, finally, it will be shown how this power theory of capital will be used to analyze capital accumulation in the pharmaceutical sector.

2.1 The Productivity Doctrine in Standard Economics

Is knowledge becoming central in the process of capital accumulation? This question is far from easy since it implies that we all mean the same thing when we discuss capital accumulation. As strange as it may seem, "capital" has no accepted definition in economics. In the middle of the nineteenth century, Nassau Senior (1854) expressed a feeling broadly shared among economists: "Capital has been so variously defined, that it may be doubtful whether it has any generally received meaning". At the turn of the century, Irving Fisher (1896, 300) arrived at the same conclusion:

> Were it not for the indomitable faith which every economist and business man feels that capital is something real and definite, one would be strongly tempted to conclude, from the repeated failure to fit any formula to it, that it is incapable of exact and scientific meaning, and that the best course for economists to pursue is simply to relinquish the search as for an *ignis fatuus*.

Eugen Böhm-Bawerk attempted to fix the meaning of capital for analytical purposes in economics through his constantly revised review of the literature about capital (Böhm-Bawerk 1884-1909). The undertaking was far from easy: Böhm-Bawerk identified 45 different theories of capital, and subdivided them into what he considered to be five incompatible categories. Far from fixing any authoritative meaning to the concept of capital, Böhm-Bawerk caused huge controversies over the meaning of the concept, involving figures such as Thorstein Veblen, Irving Fisher, Frank Fetter and John Bates Clark. The twentieth century also rendered less than definitive meanings. While neoclassical economists,

following Paul Samuelson, fixed the concept in the production function, the Cambridge controversies[4] (Harcourt 1972; Cohen and Harcourt 2003) over the nature and measure of capital forced neoclassical economists to admit that their conception of capital, measured by its marginal productivity, was simply inconsistent. However, without an alternative that could fit their theoretical edifice, they chose to leave unchanged their conception of capital, acting "as if" they had a consistent theory and maintained a "surrogate" production function to measure capital through its productivity (Burmeister 2000).

The confusion over the concept of capital remains intact in the contemporary era. Capital can imply "means of production", "roundabout process of production", "invested sum of money", "actualized value of a stream of income", "abstinence over consumption" or a "wage-fund". It can be an economic power, an economic actor or a complex social relationship allowing the exploitation of the working class. While space does not allow for a full treatment of this debate, which goes back at least to Turgot and Adam Smith, it is possible to classify perspectives on knowledge capitalization by their responses to two questions:

i) Is the earning-capacity of capital determined by its productivity?

ii) Is knowledge a productive form of capital?

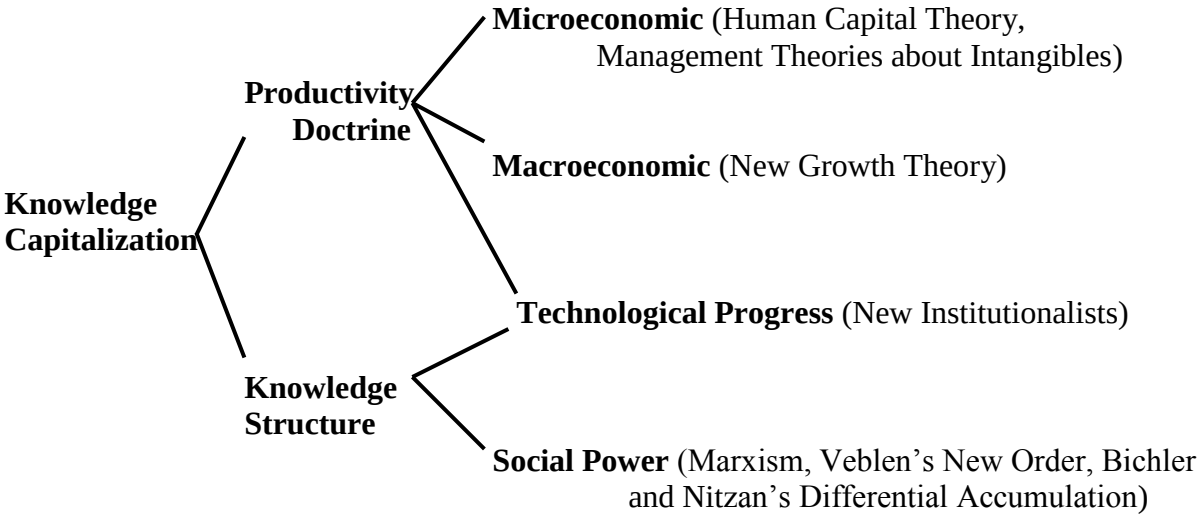
[4] The Cambridge Capital controversy has been an important debate in economic theory in the 1960s concerning the nature and role of capital goods. The debate was largely between Post-Keynesian and Neo-Ricardian economists, such as Joan Robinson and Piero Sraffa, and neoclassical economists, such as Paul Samuelson and Robert Solow. The name of the controversy comes from the location of the main participants to the debates: The firsts were from the University of Cambridge (UK), and the others came from the Massachusetts Institute of Technology in Cambridge (USA).

As a discipline, economics has been built on answering "yes" to the first question, implying that, normally, profits are the counterpart of production. This "productivity doctrine of capital"[5] is central to standard economics nowadays since standard economic theories still endeavor to explain value and distribution from the realm of production, by determining income based on output (Commons 1934; Hausman 1981; Bichler and Nitzan 2000). Such an approach, to say the least, is problematic and must be questioned because it is based on an ideological premise, according to which the gains of capital is the logical counterpart of its productive contribution to society. The consequence of such premise is that the growing earnings of capital observed since the beginning of the 1980s, due to neoliberal restructuring, are considered to be as the result of greater production. Such claim is far from evident. For example, David Harvey (2006, 43) claims that the "main achievements of neoliberalism have been redistributive rather than generative". Specifically, the analysis of the distribution of social power shows that the growing earnings of capital in the neoliberal era has been first and foremost the result of the redistribution of power in favor of capital and at the detriment of workers. A study by Citigroup (Kapur et al. 2006, 2) confirms this state of affairs: "Despite being in great shape, we think that global capitalists are going to be getting an even greater share of the wealth pie over the next few years, as capitalists benefit disproportionately from globalization [...] at the relative expense of labor". By analyzing the phenomenon of the distribution of social power, the earning-capacity of capital cannot be considered only as being determined by its productivity.

[5] "Productivity doctrine of capital" is the preconception in economics according to which earnings of capital are a counterpart for the social wealth it produced.

As for the second question, traditional economic literature normally avoided the possibility that knowledge and capital might relate, thus ignoring altogether the cognitive dimension of the economy. Such analyses simply considered knowledge not to be part of political economic analysis. Knowledge was considered as exogenous, as something given. While some economists prefer to stick with old models, in which knowledge cannot be capitalized as such, an important literature in standard economics has developed in recent years, considering knowledge as new intangible means of production in late capitalism. For purpose of clarity, it is possible to classify the different approaches to the link between knowledge and capitalization. Approaches can be divided between those that integrate the productivity doctrine of capital and those that refuse the productivity conceit and focus, instead, on the knowledge structure that allows such capitalization. Some approaches also share both arguments (Figure 2.1).

Figure 2.1: Taxonomy of Approaches to Knowledge Capitalization

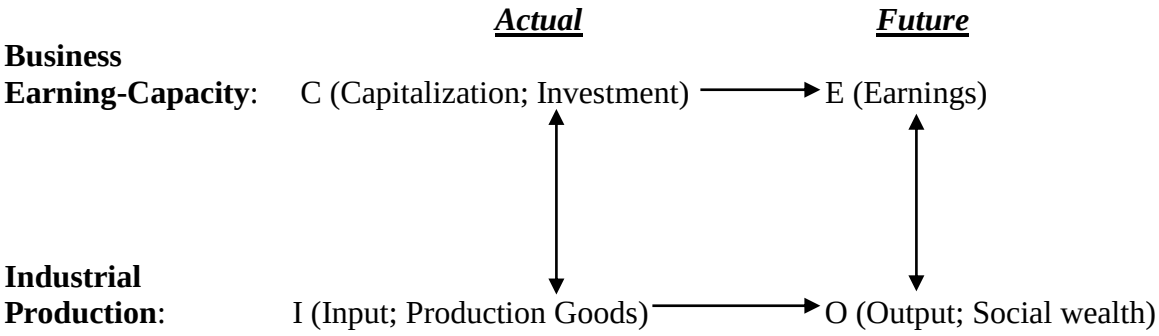


Most theoretical attempts to account for knowledge capitalization are based on the productivity doctrine of capital, which can be dated back to Adam Smith's construction of the capital concept.[6] Some approaches analyzed the knowledge structure (see below), with or without integrating the productivity doctrine. For Adam Smith (1776, Book 1, Chap.VI), capital, or stock, is simultaneously a social productive capacity (means of production) and a private earning-capacity for its owner. To maximize his private earning-capacity, the capitalist must thus maximize his social productivity. Therefore, under social institutions allowing competition between producers, an *invisible hand* ensures that the search for self-gain is the best way to serve the public good. As Friedrich Hayek (1988, 99) bluntly puts it: "When the market tells an individual entrepreneur that more profit is to be gained in a particular way, he can both serve his own advantage and also make a larger contribution to the aggregate".

Since the time of Adam Smith, this relationship between (and confusion of) private earning-capacity and social productivity, between business capital and means of production, have been the source of one of the most important ideological biases of political economy. According to this conceit the market will ensure that greater profit becomes equivalent to greater production of social wealth (Commons 1934; Gagnon 2000). Building on a figure first provided by Fetter (1914, 85), one could represent the productivity doctrine of capital as a relation between two different planes: Business earning-capacity and industrial production (Figure 2.2).

[6] See for example Böhm-Bawerk (1959 [1884-1909]), Fisher (1896) and Meacci (1989).

Figure 2.2: The Productivity Doctrine of Capital



The temporal relation between 'C' and 'E' indicates the business logic between an investment (its capitalized value) and anticipated future earnings. The temporal relation between 'I' and 'O' indicates the industrial logic between today's means of production producing tomorrow's material output and social wealth. The productivity doctrine of capital considers that industrial productivity determines the earnings of business capital: an investment has to take the form of means of production producing social wealth. The social wealth created determines the earnings of capital. The *flow* of earnings is determined by the *stock* of production goods. This productivity doctrine of capital takes different forms under different theories about knowledge capitalization.

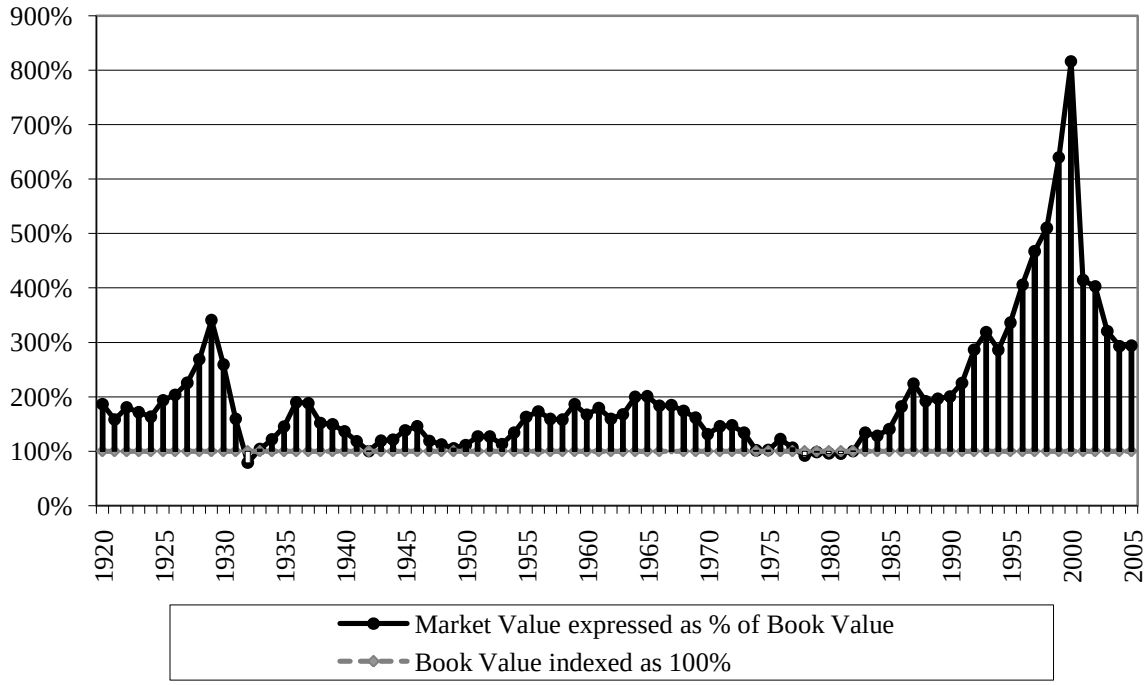
Standard economic analysis, usually defined as neoclassical economics, remains a diverse approach combining many perspectives and theories, such as the micro-economic textbook approach, the macro-economic "New Growth" theories and Neo-institutional economics. Neoclassical economists normally accept the productivity doctrine of capital since it is implied in the premises of the analysis. Because of such premises, when it comes

time to analyze the earning-capacity of knowledge, they assimilate capitalization of knowledge with the capitalization of means of production. From a microeconomic point of view, the productivity doctrine of capital means that one can buy or use units of knowledge as a form of production good. For example, Gary Becker's (1962) theory of human capital considers that greater knowledge and education allow one to achieve a higher income; individuals are thus receptacles of knowledge, and they each decide rationally how much they invest to obtain knowledge and education so as to receive greater future incomes. Individuals thus invest in the acquisition of knowledge, understood as a production good, that then allows them to be more productive, thus ensuring them greater earnings.

Since the late 1990s, a large portion of management literature that defends the emerging "New Economy" or "knowledge-based economy" (KBE) has made intangibles (understood as capitalized knowledge) the main assets of firms, on the grounds that a firm's capacity to make a profit depends more and more upon its capacity to innovate (Webster 2002; Corrado & al. 2005). Knowledge is thus understood as units of intangible assets, in which firms invest for greater earning-capacity. In this vein, accountants such as Baruch Lev (2001; 2003) and Karl-Erik Sveiby (1998) view the widening discrepancy between a company book value (outlays for capital appearing in the balance sheet) and–market value (actualized value of anticipated earnings as determined on the stock market) to be the result of the growing importance of new productive intangible or intellectual assets. This "intellectual capital" does not appear on the companies' balance sheets. According to Sveiby, figure 2.3 shows intangible assets made of knowledge (or other immaterial means of production) as the discrepancy between market-to-book values. While figure 2.3 displays the burst of the technological bubble in 2000, the market-to-book value, even after the collapse in the stock

market, remains almost as high as it was at the verge of the 1929 crash. As Lev explains (2003, 17), even in the event that the market-to-book value falls as low as 300%, "it would be sufficiently higher than it was in prior periods, and high enough to confirm that an amount of value equal to between one-half and two-thirds of corporate market values reflects the value of intangible assets".

Figure 2.3: Intangible Assets as % of Tangible Assets
« Market-to-Book Value » for Dow Jones Industrial Average, 1920-2005



Source: Sveiby (1998), Data updated with Value Line.

Sveiby's and Lev's interpretations remain, at the least, dubious. The discrepancy between market-to-book values is simply explained away by assuming that if existing means of production do not account for increasing capitalization, then a new intangible, immaterial

means of production, invisible in the balance sheet, 'must' exist. "Knowledge" is the *ad hoc* element being brought in to fill the gap. Knowledge is reduced to "intangibles" that can be used and sold as traditional physical capital. It is surprising, however, to see how knowledge and intangible capital can so quickly appear and evaporate, to see how quickly firms can lose their accumulated knowledge. It is also surprising that productive human capital, which belongs by definition to workers, is capitalized here by firms instead of workers.

Also, it is not clear at all why those intangible assets have to be assimilated with productive knowledge. For example, some authors consider, instead, that those intangibles should be assimilated with firms' monopolistic capacities (Hughes 1982; Lindenberg and Ross 1981). In fact, the suggestion that only knowledge explains firms' inflated market value does not further our understanding; it is an ideological construction based on the arbitrary assumption that business earnings 'must' be related, somehow, to industrial productivity. As such, since economic reality contradicts economic theory, advocates of the microeconomic approach to knowledge capitalization simply presume an invisible reality that cannot be seen or analyzed, and this invisible reality arbitrarily "explains" the existence of new earning-capacities. This evasive construction serves only to discard any other possible explanation, and to preserve the foundations of standard economics.

In the economic literature about the pharmaceutical sector, most micro-economic arguments related to knowledge capitalization take for granted the productivity doctrine of capital by considering knowledge to be an intangible asset taking the form of 'human capital' (Vey and Cantrell 2004), 'knowledge-capital' (Lichtenberg 2005) or intellectual property rights (Bosworth & Mahdian 1999). By extension, one could include under the same label the different papers that argue that high profitability in pharmaceuticals is due mostly to

increased innovation (Baily 1972; Calfee 2000; Oppenchaim 2001) or by the increased amount spent in R&D (Grabowski and Vernon 1990). As will become apparent below, by contrasting the declining innovation and the rising profit in the pharmaceutical sector in recent years, it is worth rejecting on empirical grounds such micro-economic neoclassical approaches because they do not help to understand the reality behind existing data.

Some neoclassical authors propose, instead, a macroeconomic approach to "endogenous growth", which makes the growth of knowledge (or technological change) a constituent part of economic growth. Knowledge is, thus, a shared social reality, not an individual's possession. Making technology endogenous to growth has thus brought endogenous growth theorists to reject, and then completely redefine, the old notion of capital so as to make it a social entity (McCormick 2002). For example, Paul M. Romer (1986, 1003) presents a model that considers knowledge to be the basic form of capital, and Robert Lucas considers human capital critical as an engine of growth. Lucas (1988, 19, italics in the original) even emphasizes the social nature of knowledge and insists: "human capital accumulation is a *social* activity, involving *groups* of people in a way that has no counterpart in the accumulation of physical capital". This approach could be of great interest if it was not for the way it falls back on the microeconomic pitfalls. The "new growth" (endogenous growth) theories attempt to integrate knowledge with economic growth by enlarging the traditional production function to include knowledge beside labor and capital. The problem is then to define "knowledge" as to measure it in terms of units of inputs. Some authors define it as R&D expenditures (Romer 1990), human capital (Lucas 1988) or the "fraction of labor force in universities" (Mankiw 1995). Basically, for the new growth theories, the growth rate of knowledge is determined by the existing stock of knowledge as well as the amount of labor

spent in acquiring knowledge. Such a theory can preserve the neoclassical function of production, measuring the marginal productivity of every unit of capital, thus preserving the productivity doctrine of capital. Putting aside the fact that, as an analytical tool, the production function has been shown to be logically inconsistent since the 1960s[7], the problem with this approach is that it attempts to reduce technological change to converting units of "inputs" into more units of "outputs". Such approach falls short of understanding the process of technological change, since technology is reduced to quantitative units. As McCormick (2002, 274-275) explains, new growth theorists did not yet understand the nature of technological change:

> Technological change is not a commodity to be produced; rather it is a change in how people think. And this change in thinking is not *only* the acquisition of more scientific facts; it is also a change in habits of thought. […] Hence even at the most abstract level, one cannot speak in terms of production functions for technology, because the output transforms the inputs; it is therefore not clear which is which. […] The process of technological change is nothing less than a process of cultural transformation.

The claim of the emergence of a "New Economy", or of a KBE, is related to the idea purported by new growth theories that knowledge has become the new intangible asset mostly responsible of economic growth. The productivity doctrine of capital, by presuming the causes before analyzing the facts, impedes a real understanding of the actual technological transformations in capitalism. Specifically, this doctrine incorporates two important ideological biases that need to be identified; two self-evident "truths" that need to be questioned. First, approaches that draw upon the productivity doctrine imply that

[7] Debates about the neoclassical function production, usually referred to as the Cambridge controversies, have been well documented. For a general presentation, see Harcourt (1972), Hausman (1981) or Jorland (1995).

knowledge is a privately-owned commodity input that produces a privately-owned commodity output called knowledge. Instead of describing the endogenous process of economic growth, it prescribes implicitly that this growth must be achieved through commodification of knowledge, which is neither "natural" nor "normal". It is, instead, the result of a political will[8]. As Herrera and Vercellone (2003, 48-49) note, those approaches curiously coincide with the unprecedented extension of IPR in the corporate arena, as if such rights were natural and necessarily beneficent for the whole society. When knowledge is considered to be a tradable asset that can be privately owned, there is no analysis of the existing and evolving knowledge structure that allows such privatization; it is simply considered natural and unavoidable.

Second, approaches claiming the emergence of a KBE are normally based on technological determinism, which is an ahistorical, positivist view that technological transformation is, through the competitive imperative, the prime factor that causes historical change, forcing the transformation of society along a predefined and inescapable path. According to this point of view, however, the "New Economy" has not been achieved totally. Instead, it is a work-in-progress and we are in a transition phase between the old industrial economy and the new KBE, in which new technologies force the adaptation of firms and societies. The political will to ensure the transition to the KBE is particularly clear in countries like Australia, Canada, Europe, Israel and, especially, the United States. For instance, the U.S. *Economic Report of the President 2001* focused entirely on institutional

[8] This political will to commodify knowledge through intellectual property rights is usually presented as a trade-off between innovation and diffusion of knowledge so as to favor the greater public good. However, the greater public good is itself an object of political debate. For example, one can define the public good in terms of domestic economic growth, while others can see it in terms of the extension of life expectancy in developing countries.

changes believed necessary in order to make the "New Economy" a durable reality, such as the extension of intellectual property rights (IPR). The "New Economy" thesis thus becomes an ideological discourse, anchored in technological determinism, demanding the necessary adaptations of institutional structures to the imperatives of new technologies and economic growth. The similar concepts of the rise of a network society (Castells 2000), of a knowledge-based global economy (OECD 1999) or of an age of access where markets give way to networks (Rifkin 2000) share the same technological determinism, in which new technologies impose specific social transformations.

2.2 The Institutionalist Path: Knowledge as Power Structure

The institutionalist approach provides great insight about how to theorize capital and knowledge capitalization without falling back on the productivity doctrine of capital. This dissertation thus follows the institutionalist path to analyze knowledge capitalization, and builds mostly on the works of Thorstein Veblen, Jonathan Nitzan and Shimshon Bichler. The word "institution" is itself very ambiguous as it was used in very different ways in the realm of social sciences since at least Giambattista Vico's *Scienza Nuova* of 1725. There is still no unanimity about the meaning of this concept; so in order to introduce an institutionalist approach, it is necessary to identify first what "institutions" mean.

By focusing on institutions, it is taken for granted that much of human interaction and activity is structured in terms of overt and implicit working rules that shape habits of thought and human conduct. Following Geoff Hodgson (2006, 2), "institutions" may be defined as

"systems of established and prevalent social rules that structure social interaction". This definition is very similar to Jack Knight (1992, 2) who defined "institutions" as "a set of rules that structure social interactions in particular ways". Along these lines, language, rules of property, money, law, table manners, habits of thought and firms are all institutions. Institutions structure social interactions and thus create stable expectations of the behavior of others by enabling ordered thought, consciousness and action. Institutions provide meaning and purpose to human actions. All human actions are teleological: they have a purpose for the social agent. For example, Karl Marx (1887, chapter 7) considers that the teleological purpose of human actions is what distinguishes man from animal:

> [W]hat distinguishes the worst architect from the best of bees is this, that the architect raises his structure in imagination before he erects it in reality. At the end of every labor-process, we get a result that already existed in the imagination of the laborer at its commencement. He not only effects a change of form in the material on which he works, but he also realises a purpose of his own that gives the law to his modus operandi, and to which he must subordinate his will.

Such teleological actions do not mean that the development of the community, or history, is teleological. It means only that when an agent acts, it is because he has an intention[9]. Because of the possibility of unintended consequences, however, the results of the actions may be far from the intention behind it. All actions are teleological, and it is contended here that, for social agents, their purpose is the result of existing institutions. By embedding and structuring social interactions through working rules, institutions do not only constrain; they make behavior possible by enabling choice and purpose and by offering

[9] For the sake of briefness, tropisms, such as the unintentional action of taking out your hand of boiling water, are excluded here from the analysis.

procedures and means to achieve their purpose. For example, as a social institution, language is a set of rules that allows us to communicate by constraining ideas into a communicable form. A social institution is both a system of constraints and a configuration of possible actions; it interweaves human possibilities and social control. Social institutions are embodiments of social power, but, as Michel Foucault puts it (1975, author's translation): "We must cease once and for all to describe the effects of power in negative terms: it "excludes"; it "represses"; it "censors"; it "abstracts"; it "masks"; it "conceals". In fact, power produces; it produces reality".

Alan Wells (1970, 3) suggests that "[s]ocial institutions form an element in a more general concept, known as social structure". For authors from the "old school" of institutional economics such as Thorstein Veblen and John R. Commons, institutions are also a type of social structure with the potential to change agents in their purposes or preferences. In fact, for Veblen (1899, 190): "The institutions are, in substance, prevalent habits of thought with respect to particular relations and particular functions of the individual and of the community". If institutions are all part of the social structures, the opposite is not true since some social structures, such as the demographic structures, construct and constrain social possibilities, without mobilizing rules and habits of thought. Institutions, defined as rules or habits of thought, do not need to be strictly followed. They can be criticized and transformed. However, since institutions work only because the rules involved are embedded in shared habits of thought and behavior, they possess a strong conservative dimension[10]. Hodgson (2006, 7) explains: "Habits are the constitutive material of institutions, providing

[10] Veblen (1899, chapter 8) considers also that the main reason for institutional conservatism is because the ruling elite (the leisure class) benefits from existing institutions and accepts to modify them only if they are forced to do so in order to best preserve their vested interests.

them with enhanced durability, power, and normative authority. […] Accordingly, institutions are simultaneously both objective structures 'out there' and subjective springs of human agency 'in the human head'".

For some authors, such as Douglass North (1990, 3), institutions are defined more as objective structures "out there"; they are "rules of the game" or "humanly devised constraints". For others, such as Veblen, institutions are, instead, "in the human head" as they are defined as prevalent habits of thought. Veblen (1909, 628-630) also argues that the institutional fabric (out there) and habits (in the head) are mutually interlaced and reinforcing. This dissertation follows the path proposed by "old" Institutionalists, such as Veblen and Commons, for whom institutions are rules socially imposed on individuals, and internalized in the mind of the agents.

Importantly, however, such an institutionalist approach to society is not a structuralist approach, in which social structures determine every aspect of human life. While the existence of dominant institutions must be acknowledged, there can be alternative institutions, or different aspirations or modes of action that can put into question dominant institutions and attempt to transform them. From a pragmatist perspective, knowledge and habits of thought do not exist because they are true or good in the absolute, but because they are well fitted to the material environment under which social agents live. The constraints of the material milieu should not be understood here in terms of material exigencies for survival, but, instead, as material exigencies to maintain or increase social recognition. The struggle for survival should be interpreted, as Veblen (1892) terms it, as "a struggle to keep up appearances". Social agents, such as individuals or organizations, act according to habits of thought determined in part by the exigencies of material milieu. Nonetheless, the material

milieu is itself determined by the actions of social agents. Actions can transform, consciously or not, the material life of a community in such a way that it will transform existing habits of thought that provide purpose for action. Social agents can also aim at transforming directly institutions and habits of thought for example through militant actions, by voicing their opinion, or through massive marketing in the case of a corporation[11].

In this way, the institutionalist perspective opens the door to a real possibility for human agents to intentionally transform the existing dominant institutional structures. Agents do not simply react to outside events; they can purposefully transform the world and the structures in which they live. Veblen, for example, emphasizes this point and mocks standard economic theory, which considers the individual to be a "homogeneous globule of desire" (1898a, 389), passive and inert. According to standard economics, the individual simply reacts to the impulse of stimuli, but when the force of the stimuli is spent, the individual comes to rest without being transformed in any way during the experience. From an institutionalist perspective, the social agents become the prime movers of the process of living; they can attempt to transform consciously habits of thought, or the material milieu, which, in turn, will also transform social agents. Far from being a structuralist perspective, such an institutionalist approach integrates analytically far greater possibilities for human freedom than the methodological individualism of standard economic theory, which claims to champion individual freedom to understand the world in which we live.

In the analysis of the institutional evolution of the social structures, 'Old' institutionalism must be clearly distinguished from 'New' Institutionalism (Hodgson 1993b).

[11] Veblen (1908d) provides one the first analysis of the economic impact of advertising, and shows for example how a corporation can act in order to transform prevailing habits of thought in order to increase its earning-capacity.

The New Institutionalists, such as North (1990), Williamson (1985) or Nelson & Winter (1982), also contend that technological advance is not a cause, but a consequence of social transformations, since the socio-institutional setting determines the path of technological development. Through economic competition, the firms and institutions that most efficiently organize, produce and use this technological development will gain an advantage, which allows a selection of the fittest institutions that then become the new point of departure for path-dependency[12]. The problem is that this path-dependency approach, which is normally shared with neo-Schumpeterian and neo-Hayekian advocates of evolutionary economics, falls into a "Panglossian"[13] trap (Hodgson 1993a, 197-213). The New Institutionalists are prisoners of an analytical framework that considers that if something exists in the economy, it exists so because it is most efficient. For example, since Coase (1937), Neo-institutional economists have considered that firms exist only because they provide lower transaction costs than markets do. In fact, the existence of any economic institutions, like property rights, corporations or the form of corporate governance can thus be explained by its economic efficiency (North and Thomas 1973; Williamson 1985)[14]. While they do not consider knowledge to be capital *per se*, the way firms manage it to produce and innovate allows them to be more or less competitive compared to their rivals. For example, the firm's management of knowledge – its routine – becomes its main capacity to build an advantage over others

[12] The notion of path-dependency refers to the fact that both the starting point and accidental events can have significant impact on (historical) outcomes. For a more technical presentation of path-dependency and how it applies to economics see David (2000).

[13] Dr Pangloss, a character in Voltaire's *Candide*, and a caricature of Leibniz, posits that everything is always for the best: "[T]hings cannot be otherwise than as they are; for as all things have been created for some end, they must necessarily be created for the best end […] and they, who assert that everything is right, do not express themselves correctly; they should say that everything is best" (Voltaire 1759, Chapter 1).

[14] North (1990) nevertheless changed his opinion, and now accepts that inefficiency in economic institutions is possible and can be reproduced. Such inefficiency, however, remains an exception to the norm, just as monopolies are exceptions to the perfect competition of neoclassical economics.

(Nelson & Winter 1982) and market competition selects the fittest ones. The New Institutionalists are thus still caught in the productivity doctrine, under which firms are seen to capitalize their routines – or organizational capital – to manage and produce knowledge, but in such a way that greater capital still means greater productive capacity. Such an approach must be discarded because the power dimensions of the social structures remain simply ignored.

The 'old' institutionalist approach rejects entirely the preconception of economic efficiency of existing institutions, contrary to neo-institutionalist perspectives. By suggesting that they are selected and reproduced socially via a struggle to keep up appearances, institutions can be totally inefficient in economic terms, since social recognition can be achieved through actions favoring emulation over efficiency. Veblen's *Theory of the Leisure Class* (1899) can be considered as the catalog-form enumeration of "imbecile" institutions in the age of corporate capitalism, such as the women's corset (172), varieties of dogs "bred into grotesque deformity" (141), or the content of higher education favoring elite culture over a matter-of-fact understanding of the world (363-400). Veblen emphasizes particularly the imbecility of the obsolete institution of private property, which defines justice in the distribution of wealth based on individual merits, and which considers capital's earning to be the counterpart of its productive contribution. This, he argues, is counterintuitive in a system of corporate capitalism dominated by absentee owners, who accumulate great wealth without participating in the process of production, amassing their fortune, instead, through the sabotage of production.

In his analysis of the leisure class, Veblen asserts that if institutions evolve constantly, a central task is then to identify the social agents that aim to restrain this process of evolution.

The answer is simple: the power elite (or the leisure class), which benefits from existing dominant institutions, will do anything they can to direct (or impede) their social evolution, since they bolster vested interests, and enforce their capacities to get "something for nothing". The ruling elite, and particularly businessmen, maintains important social ascendancy over the dominant institutional framework since they control the reins of power. They also embody the standards of honor and beauty, which the rest of the population tends to emulate (Veblen 1899, Chapter 6). The social evolution of dominant institutions becomes, in fact, a selection of habits of thought by the social elite, which accepts institutional innovation and evolution only if (1) they have no other choice when facing the possibility of important social fractures that could give rise to more radical institutions more adverse to their vested interests, or (2) if they can benefit more from the new institutions. Far from being a theory that explains the economic efficiency of institutions, such as the neo-institutionalist approach, the "old" institutionalist approach is, instead, a theory aimed at explaining the constant economic inefficiency of the institutional framework that serves the interests of the social elite. As Veblen (1899, 207) bluntly puts it:

> The characteristic attitude of the [leisure] class may be summed up in the maxim: "Whatever is, is right"; whereas the law of natural selection, as applied to human institutions, gives the axiom: "Whatever is, is wrong." Not that the institutions of to-day are wholly wrong for the purposes of the life to-day, but they are, always in the nature of things, wrong to some extent.

Avoiding structuralist and Panglossian traps, the 'old' institutionalism offers both important theoretical insights and a space for social critique. The social structures should not be understood in terms of best-fitted social institutions that emerge through technological

determinism; instead, it becomes necessary to analyze the ascendancy of business interests over those institutions.

The Knowledge Structure

From an institutionalist perspective, contemporary technological transformations are not the prime mover of the process of economic transformation. To analyze such process, one needs to understand the workings of socio-institutional settings that allow technological development to take its actual form. By focusing on the capitalist dimension of economic institutions, the nature and the form of technological transformations become the result, rather than the cause, of socio-economic transformations. Technology and knowledge can be analyzed through what Susan Strange (1988, chapter 6) calls "knowledge structure", referring to social structures in which technology and knowledge are embedded, and that is shaped and determined by myriad social processes and by human agency.

Knowledge structure denotes the overall social institutions that shape the production and diffusion of knowledge. This concept redefined the concept of power in International Political Economy (IPE). The dominant neorealist approach in IPE analyzes the distribution of power between nations, and considers that power is relational since it is expressed through relations between actors and relies on might and capacities. Against this exclusive concept of "relational power" used by neorealists, Susan Strange develops the concept of "structural power" (Strange 1988, 24-25), which is "the power to shape and determine the structures of the global political economy within which other states, their political institutions, their economic enterprises and (not least) their scientists and other professional people have to operate". According to Strange, structural power means more than simply the power to set

the agenda[15]; it is the power to shape frameworks within which actors relate to each other. For Strange (1988, 26), structural power is to be found, not in a single structure, but in four different intertwined structures. The four sources of structural power are control over security, control over production, control over credit and control over knowledge. From those four sources emerge the four power structures: Security, production, finance and knowledge. Strange considers that all four structures are equally important, but that knowledge structure has usually been the one that has been most overlooked and underrated.

Knowledge structure includes all structures that shape the production and diffusion of technological knowledge. In the IPE literature, Neo-Marxists and Neo-Gramscians, such as Robert Cox (1987) and Stephen Gill (2002), normally emphasize the importance of the production structure and the class relations implied in the production process. With Christopher May (2000, 30), however, it must be granted that knowledge "production" has become an "economic" activity through the commodification of knowledge and that "the distinction between knowledge and production structures to some extent starts to break down". Strange's taxonomy thus needs to be adapted and it will be considered here that the concept of "knowledge structure" also includes the "production structure".

Knowledge structure includes the beliefs, habits of thoughts and the social channels – including the social relations of production – by which beliefs, ideas and knowledge are produced and communicated. Knowledge structure is thus the "established" way to produce and diffuse knowledge in a way that will be accepted by social agents. It thus refers not only to technology and knowledge, but also to the institutional structure, or "ceremonial

[15] Strange aims here at criticizing Lukes (1974) who considers that structural power is the power to set agenda, which is the power to circumscribe choice in such a way that the limitations of choice is not perceived as such by the actors in social relations.

encapsulation" (Waller 1987). Knowledge structure, which stresses the normative aspect of all structural power, becomes quite similar to the concept of hegemony used by Neo-Gramscians (Gill 2002) to identify all the ramifications of the ruling ideology. An important difference, however, is that Neo-Gramscians derive the ruling hegemony primarily from a class analysis (from the production structure). The knowledge structure is certainly shaped to a great extent by the ruling class, but this ruling class is not homogeneous, and the knowledge structure is also shaped by the conflicts that arise inside the ruling class, and also through contingency and path-dependency phenomena.

Knowledge structure, as defined here, is the combination of social and material structures shaping and determining the production and transmission of technical and cultural knowledge. The knowledge structure concept is essential to understanding how the institutional settings can allow dominant firms, for example, to gain control over knowledge in any sector, and transform it into earning-capacities. Specifically, in the case of pharmaceuticals, the knowledge structure is based mostly on the production of commodified knowledge in research laboratories and through clinical trials. Pharmaceutical knowledge is diffused through many channels, such as scientific journals, continuing medical education and channels of aggressive promotion towards physicians. The knowledge structure is the multiplicity of all power relations immanent in the way knowledge is produced and transmitted. This concept remains very broad, but, in the coming chapters, it will be used to include every dimension of pharmaceutical firms' control over their sector that can translate into earning-capacities. This definition does not reduce the knowledge structure to an outgrowth of the mode of production, and certainly not into a social structure that is "determined" by existing technologies. It allows an analysis of socio-institutional settings

from a broader institutional perspective, where knowledge structure is determined, not only by the ruling class, but also by contingency, path-dependency and struggles between all social actors, including struggles among the ruling class.

2.3 Capitalizing Institutional Power: Veblen's Theory of Capital[16]

"Some of [Veblen's] students discovered in physical combat
that he was not as weak as he appeared."
- Joseph Dorfman

Analyzing the American economy at the beginning of the twentieth century, Thorstein Veblen contended that knowledge has always been the main productive economic asset. Veblen also analyzed the ways and means of industrial control by business interests during the era he calls the New Order.[17] He considers that control over industrial knowledge, and over the material means to put this knowledge to use, constitutes the core of capital's earning-capacity as a form of control over the community. From a Veblenian point of view, capitalism's contemporary transformations should not be viewed in terms of new forms of productivity but, instead, in terms of the new ways and means for business interests to extend their control over the knowledge structure, in the way it was defined earlier.

[16] A shorter version of this section has been already published in the *Journal of Economic Issues* (Gagnon 2007).

[17] By *New Order*, Veblen refers to the new business order that emerged in the era of robber barons, when industries organized into corporations, cartels and trusts. This *New Order* is characterized by the collectivization of capital in business enterprises and absentee ownership of corporations.

Concatenated Industry and Parasitic Business Sabotage

Between 1904 and 1908, Veblen analyzed the concept of capital in economics. His major work on the topic was his *Theory of Business Enterprise* (1904), in which he offered an inductivist concept of capital, based on the nineteen volumes of the Report of the Industrial Commission (1900-1902), which, in the wake of anti-trust laws, aimed at getting to the bottom of actual business practices in the American economy[18]. From the report, Veblen brought to light an economic world divided into two levels: 1- An industrial level in which networks of production and industrial systems are more interconnected and efficient; 2- a business level in which businessmen's discretionary powers over industry is rising due to new forms of property, such as corporations and trusts.

At the industrial level, Veblen observes that industrial production is now based on networks where there is a growing concatenation of industrial sectors (1996 [1904], 15-16):

> [C]oncatenation of industries has been noticed by most modern writers. […] the prevalent standardization of industrial means, methods, and products greatly increases the reach of this concatenation of industries, at the same time that it enforces a close conformity in point of time, volume, and character of the product […] By virtue of this concatenation of processes the modern industrial system at large bears the character of a comprehensive, balanced mechanical process.

Because of the great technological proficiency and productivity of the concatenated industries, Veblen's analytical starting point is that of an affluent society – a society in which the maximum use of productive resources would create abundance (or, in economics terms, an overproduction crisis). This starting point contrasts with the postulate of scarcity that we

[18] In his *Theory of Business Enterprise* (1904), Veblen constantly refers to this report, particularly Volumes I and XIII, which analyze trusts, business combinations and the evolution of cartels' share prices while setting forth an impressive compendium of testimony by businessmen and financial magnates. The *Theory of Business Enterprise* is in fact a theoretical synthesis of the *Report of the Industrial Commission*.

find in standard economic analysis, where value is examined in the relation between man and nature and is measured as the productive effort over nature, as the "toil and trouble" necessary to free ourselves from scarcity[19]. In Veblen's view (1899, chapters 2-4), it is pecuniary emulation among individuals and conspicuous consumption that cause scarcity. Scarcity does not exist in the absolute due to limits imposed by nature but, instead, rests on human relations and the institutional struggle to keep up appearances based on the differential logic of pecuniary rivalry. In short, scarcity is artificially constructed by elites so they can benefit from greater social distinction. Value must thus be analyzed as a power relation between men; the creation of value rests less on the creation of wealth than on the creation of scarcity.

On the other hand, if concatenated industries are now more efficient, the industrial system is not self-regulated. In fact, it is controlled by the social elite that Veblen variously identifies as the "leisure class" (1899), "vested interests" or "kept classes" (1919b). In the era of corporate capitalism, which Veblen calls the "New Order", the social elite that controls the industry and the community is mainly composed of absentee owners (1923), or more generally by businessmen (1996 [1904], 2-3):

> The business man, especially the business man of wide and authoritative discretion, has become a controlling force in industry, because, through the mechanism of investments and markets, he controls the plants and processes, and these set the pace and determine the direction of movement for the rest. […] His control of the motions of other men is not strict, for they are not under coercion from him except through the coercion exercised by the exigencies of the situation in which their lives are cast; but as near as it may be said of any human power in modern times, the large business man controls the exigencies of life under which the community lives […] For a theoretical inquiry into the course of civilised life as it

[19] While this concept is fundamental to the classical theory of value (Smith 1991 [1776], Chap. V; Ricardo 1996 [1817], Chap. I), it is also considered by neoclassical economics to be the determining principle of the supply curve (Marshall 1952 [1890], Book V, Chap. III; Samuelson 1958 [1948], Chap. 24).

> runs in the immediate present, […] no single factor in the cultural situation has an importance equal to that of the business man and his work.

Businessmen do not participate in production, but develop control over the knowledge structure and the community in general since business gained an upper hand on political power, but also on the habits of thought of the population. Businessmen's motives are not to maximize production, but to maximize pecuniary gains through pecuniary transactions of buy and sell. In fact, their pecuniary interests are better served by restraining production and by artificially creating scarcity. Business practices are thus predatory practices of industrial sabotage, and the business trade must be considered not as a positive or zero-sum game but as a negative-sum game (Veblen 2002 [1919a], 54-55): "[this state of affairs] has some analogy with the phenomena of blackmail, ransom and any similar enterprise that aims to get something for nothing". The businessman interferes in strategic interstices of the concatenated industrial system and, depending upon its sabotage capacity – the importance of the interstice taken hostage through his property rights, or capital – he can reclaim a more or less important ransom, which could be understood as a monopolistic rent.[20] Veblen observes that the free functioning of the industrial system would better serve the community, but not the businessmen's pecuniary interests[21]. Left in the hands of engineers, the industrial system would be in a position to satisfy the needs of the whole community. For businessmen, however, it would create an overproduction crisis with falling prices and profits. On the other hand, a businessman can obtain substantial differential gains by disturbing the interstitial

[20] For Veblen, there is no real distinction between rent and profit, since the interest on capital is essentially rent (McCormick 1989, 613).

[21] Veblen even proposed that industry should be organized and governed by a "soviet of technicians" (1965 [1921], Chap.VI), but he remained very sceptical of the possibility of such a scenario because of the conservative dimension of engineers as a social class.

articulation between concatenated industries. Perturbation of the industrial system is thus a business norm, not an exception (1996 [1904], 31-32):

> The exigencies of this business of interstitial disturbance decide that in the common run of cases the proximate aim of the business man is to upset or block the industrial process at some one or more points. His strategy is commonly directed against other business interests and his ends are commonly accomplished by the help of some form of pecuniary coercion.

Sarcastically, Veblen (1997 [1923], 65-67) identified this earning-capacity through the threat of sabotage as the "natural" right of investors:

> Any person who has the legal right to withhold any part of the necessary industrial apparatus or materials from current use will be in a position to impose terms and exact obedience, on pain of rendering the community's joint stock of technology inoperative for that extent. Ownership of industrial equipment and natural resources confers such a right legally to enforce unemployment, and so to make the community's workmanship useless to that extent. This is the Natural Right of Investment. […] Plainly, ownership would be nothing better than an idle gesture without this legal right of sabotage. Without the power of discretionary idleness, without the right to keep the work out of the hands of the workmen and the product out of the market, investment and business enterprise would cease.

It is the property rights of the businessman over some of the community's strategic industrial assets that determine his earning-capacity, which is not determined by the intrinsic productivity of the assets amassed, but on their strategic importance in relation to the entire industrial system. As an illustration, John D. Rockefeller's *Standard Oil* had at the time an important capitalization (or market value), not because it was highly productive, but because it was at the time the single corporation that controlled all American oil-refining capacities, and all other industries depended on refined oil. Clearly, such a reality means that the rate of

profit varies in each sector according to the power structures involved, and there is thus no "uniform rate of profit" in the economy (Veblen 1996 [1904], 90):

> The "ordinary rate of profits" has become a more elusive idea. The phenomenon of a uniform rate of profits determined by competition has fallen into the background and lost something of its matter-of-fact character since competition in the large industry has begun to shift from the position of a stable and continuous equilibration to that of an intermittent, convulsive strain in the service of the larger businessmen's strategy.

This dimension of Veblen's theory is of the foremost importance for this dissertation. By contending, contra standard economic theory, that there is no uniform rate of profit towards which tends the equilibrium in all business sectors, it asserts that differential profits between firms and sectors should be analyzed as an important indicator of their differential power and control over the knowledge structure.

Capitalization of Tangible and Intangible Assets

Veblen pursued his analysis on the nature of capital in four papers in 1908 where he compared his own theory with existing neoclassical capital theories (1908a; 1908b; 1908c; 1908d). Veblen also continued to develop and refine his theory of capital in his later works (Veblen 1914; 1919a; 1921; 1923). In his two papers published in 1908 on the nature of capital, Veblen reformulates his concept of capital in a more theoretical way, where he distinguishes how businessmen capitalize tangible and intangible assets.

Since man has never lived alone, the history of man has been the history of human communities, with more or less cultural continuity over successive generations (Veblen 1908c, 518). Any community possesses a body of technological knowledge, a state of the

industrial arts that he calls the "immaterial equipment" of the community, and it can be transmitted and augmented only in and by the community at large (Veblen 1908c, 520). For Veblen, productivity is social. It is not intrinsic to labor power or capital goods; it arises, instead, from the community's technology (Veblen 1908c, 521): "In any known phase of culture, this common stock of intangible, technological equipment is relatively large and complex, - i.e., relatively to the capacity of any individual member to create or to use it; and the history of its growth and use is the history of the development of material civilization". Human efforts, individuals' knowledge and material contrivances can become productive only if they are articulated to the community's immaterial equipment. Capital goods (or tangible assets) materially embody the community's immaterial equipment and are productive only to that effect; they are the material means to put to use the community's technology. If the technology changes, a once-productive material contrivance will simply become obsolete and go to the "junk-heap" because the specific technological expedients it embodies cease to be effective in the industrial community as compared to new methods (Veblen 1908c, 540). Material goods are not intrinsically productive since productivity is socially determined according to existing technology and prevalent habits of thought. Furthermore, technology is social by definition, since it can only be held and transmitted by a community, not by an individual member or household.

Then the question is: how can a capital good that embodies social productivity be the source of private income? Veblen considers that at earlier phases of technological development, the possession of material contrivances that allow an individual to put to use the immaterial equipment of the community does not bestow a differential advantage to its owner, since the material equipment is neither complex nor scarce. With the development of

the state of industrial arts and the increased complexity of industrial equipment, however, the ownership of capital goods becomes a strategic asset for its owner in order to capture or corner a part of the immaterial equipment of the community (1908c, 524):

> [A]s the technological development falls into such shape as to require a relatively large unit of material equipment for the effective pursuit of industry, or such as otherwise to make the possession of the requisite material equipment a matter of consequence, so as seriously to handicap the individuals who are not without these material means, and to place the current possessors of such equipment at a marked advantage, then the strong arm intervenes, property rights apparently begin to fall into definite shape, the principles of ownership gather force and consistency, and men begin to accumulate capital goods and take measures to make them secure.

Note that, in such passage, Veblen seems to fall into technological determinism by treating the development of technology as an "external variable", which then influence the whole institutional setting of society. This interpretation would be far-fetched since some of his works, such as *Imperial Germany and the Industrial Revolution* (1915), analyzes at length the historical, social and cultural settings that allowed the possibility of some development of some type of (matter-of-fact) technology. It would not be far-fetched, however, to consider Veblen's historical explanations a bit flimsy, and his analysis would certainly gain by integrating, for example, elements from the historical materialist literature (for example Wood 2002; Aston and Philpin 1985). For this dissertation, however, those debates about the historical explanation of the links between technological development and the rise of capitalism can be left aside. Veblen does not focus on explaining the reasons behind technological development and the concatenation of industries; he focuses, instead, on understanding the existing businessmen's control over the concatenated industrial system.

Veblen observes that, in a more developed society, the ownership and control of the material contrivances to put to use the community's immaterial equipment becomes a strategy for control over the community. Individuals with the capacity to take advantage of property rights so as to own and accumulate means of production[22] can thus capture and "corner" the usufruct of social productivity. For example, in agrarian societies, those with ownership and control over land can use their strategic advantage to reclaim a part of the usufruct, under the form of rent. With the industrial revolution and the development of large-scale industry, the ownership of industrial equipment also becomes a means of cornering the community's immaterial equipment so as to claim a part of the usufruct. The businessmen's capital becomes a central form of control over the community and social order is reorganized accordingly. In Veblen's works, "Capitalism" thus refers to the late period of material civilization, in which ownership of the industrial equipment comes to be the predominant method of engrossing the community's technology and usufruct.[23] By owning industrial equipment, one gains bargaining power with which to appropriate a part of the community's usufruct even without participating in the production process. The profit obtained by the ownership of capital goods is of the same nature as the rent obtained through the ownership

[22] There is a lot of debate about the origins of capital accumulation. While Veblen developed his own view about the "beginnings of ownership" (1898b) and the maintenance of a leisure class in spite of social evolution (1899, chap. VIII), he does not directly tackle the problem here; instead, he refers to the debates between Marx, Sombart and Ehrenberg on the subject (1908c, 534n). Whatever theory is chosen to analyze "primitive accumulation", it is possible to make Veblen's view of the nature of capital fit to it.

[23] Leftist political economists normally define "Capitalism" in a different way, based on market-dependence, competition, wage-labour and increasing productivity (see Wood 2002, 2-3). Consequently, what Veblen defines as "Capitalism" would normally be identified by political economists as "business capitalism" or "corporate capitalism". However, Veblen chose to define "Capital" and "Capitalism" based on the existing terminology of businessmen, and not on a pre-existing economic or historical theory. The contradiction between the two concepts is here more terminological than real since Veblen's works on capitalism does not contradict historical materialist approaches to the transition from feudalism to capitalism. Veblen's works simply bring new dimensions to the analysis of capitalist power in a society dominated by corporations and businessmen, for example by showing how corporations can increase profits by decreasing productivity and avoiding competition.

of land: it is an unearned income that arises due to the differential advantages of the vested interests.

The capitalization of tangible assets, that is the capitalization of the earning-capacity due to the ownership of capital goods, is determined by "the immaterial industrial expedients which they embody or which their ownership allow their owner to engross" (Veblen 1908c, 539). Thus, the control over the community through the ownership of the material means necessary to put to use the technology is capitalized. The owner that controls industrial equipment does not participate in production; instead, he specializes in business-related concerns and is disconnected from industrial production. He becomes an absentee owner.

Note that in the case of perfect competition, there would be no differential advantage associated with the ownership of tangible assets. Any attempt to benefit from this ownership position would be countered by competition and we would find ourselves in a situation of the neoclassical equilibrium under perfect competition, in which the rate of profit tends to zero. In this case, the capitalized value of the tangible assets would be determined by the actualized value of the quantity of product multiplied by its competitive price, and should thus correspond to the cost of production (or replacement) of those assets. However, in a capitalist era based on large-scale industry, production requires material equipment larger than what one can make or use; the large amount of equipment necessary for production creates inevitably a barrier to entry in any sector and the idea of perfect competition becomes simply elusive.

Large business enterprises, which he defines also as going-concerns, extend their control over the community by appropriating tangible assets but also by developing intangible assets,

which are not new forms of productivity, but, instead, monopolistic capacities in the sphere of distribution.

The control over the technological capacity of the community and control of differential gains in the sphere of distribution (goodwill, advertising, control over the distribution networks, social conventions) are the two main intangible assets for business enterprises (Veblen 1908d, 112-124). The typical intangible asset is what Veblen calls *Goodwill*. He includes under the term, not only its traditional meaning of *clientèle*, but also any monopolistic capacity that can increase the earnings of a business concern by controlling or restraining the supply of goods and services. However, he excludes from the definition any monopolistic capacity that can be owned legally (such as patents, franchises or copyrights)[24]. The emergence of corporations, trusts, pools and holdings in the American economy could thus be explained by the will to create goodwill. In fact, goodwill and intangible assets constitute "the substantial core of corporate capital under the new order" (Veblen 2002 [1919a], 74). Profitability is thus greatly determined by unproductiveness and the sabotage strategies of the businessmen. Veblen points out many business practices that allow businesses to increase earning-capacity without participating in industrial production. He shows, for example, how firms can sell their products at higher prices by organizing demand through the manipulation of mass desires (Veblen 1996 [1904], 55). Brands, reputation, controls over the networks of distribution, monopolistic capacities, protectionist regulations, government concessions, the allowed extent of labor exploitation, habits of thought, access to

[24] In his *Theory of Business Enterprise*, Veblen includes those elements under the definition of goodwill, but it seems here more consistent to distinguish those two kinds of intangible assets, as Veblen does in his later works. Note that Veblen's definition of goodwill is consistent with modern accountability, according to which *goodwill* represents the discrepancy between market value and book value at the moment of a merger or acquisition, while copyrights, franchises and patents represent different sub-categories of intangible assets. About the consistency of Veblen's definition of goodwill in the history of accountability, see Hughes (1982).

credit[25], in short all strategic possibilities that can provide differential gains become an asset for firms without participating to production.

All corporations, as going-concerns, thus capitalize both tangible assets (since a business must offer a product) and intangible assets. In the actual business regime, Veblen observes, intangible assets are a necessity for all corporations (1996 [1904], 142-143):

> When a corporation begins its life history without such a body of immaterial differential advantages, the endeavours of its management are early directed to working up a basis of good-will in the way of trade-marks, clientèle, and trade connections which will place it in something of a monopoly position, locally or generally. Should the management not succeed in these endeavours to gain an assured footing on some such "immaterial" ground, its chance of success among rival corporations are precarious […] The substantial foundation of the industrial corporation is its immaterial assets.

Corporate capitalism is thus characterized by its constant capacity to avoid perfect competition thanks to the differential advantages and goodwill enjoyed by large business enterprises. It is those differential advantages, moreover, that create a discrepancy in value between the productivity of tangible assets and the firm's capacity to engross the usufruct.

In the literature, however, Veblen's capital theory is usually presented as the capitalization of private capacities for industrial sabotage[26]. While it is true that Veblen mostly emphasized the parasitic nature of business in his later works, his overall theory of

[25] Veblen develops an analysis of the access to credit as a differential advantage in earning-capacities. Since the rate of interest on a loan is generally lower than the rate of return, any credit extension becomes a differential advantage for the firm as a going-concern. By capitalizing this differential advantage, the firm increases its capital, which allows the firm to receive even more credit. The rate of interest has no natural basis in terms of intertemporal preferences; it is a pecuniary phenomenon determined by the extension and contraction of credit (1998 [1909]). Veblen even provides an account of business cycles in terms of credit fluctuations (1996 [1904], 177-267). Keynes' theory of business cycle, for example, shows important similarities with Veblen's theory. While Keynes never cites Veblen, his personal notes show that he read carefully Veblen's works (Dostaler 2005, 166).

[26] See for example Commons (1934, 649-672), Pirou (1946, 50-79), Sweezy (1958), McCormick (1989), Nitzan (1992, 1998), Bichler and Nitzan (2000; 2002b; 2009).

the evolution of the social structure is about the institutional process of cultural growth in terms of cumulative causation (1898a; 1899). In this way, intangible assets are not only direct and indirect predatory means to restrain production, but are also any institutional settings or social structures that provide earning-capacities to business concerns. They can be "habits of life settled by usage, convention, arrogation, legislative action or what not" (1908b, 116), "preferential use of certain facts of human nature – habits, propensities, beliefs, aspirations and necessities" (Veblen 1908d, 123). Veblen goes further (1990 [1901], 311): "Whatever ownership touches, and whatever affords ground for pecuniary discretion, may be turned to account for pecuniary gain and may therefore be comprised in the aggregate of pecuniary capital." Capital is not only an instrument for sabotage; it is any dimension of human life that can translate in higher earnings for business capital.

Remember that, according to Veblen, the economic problem is not how things stabilize themselves in a "static state", but how they endlessly grow and change due to the cumulative causation between technology, the material milieu and institutions. Any institutional setting always nurtures vested interests with means to capture and control the community's usufruct. From a Veblenian perspective, corporations, trusts and holdings did not arise to serve the needs of a growingly productive industry, but, instead, to serve vested interests and to counter the high industrial efficiency that could result in abundance (or overproduction, as economists would phrase it). The emergence of corporate capitalism should be understood as the rise of an institutional regime to preserve vested interests confronted to the development of a highly productive large-scale industry. Vested interests had to develop more sophisticated forms of ownership (pools, cartels, corporations, trusts, holdings) in order to maintain their control over the community's production capacity. This account is consistent

with most critical accounts of the beginnings of corporate capitalism, such as the works of Roy (1997) or Perrow (2002).

Capitalizing Institutional Control over the Knowledge Structure

It is possible to synthesize Veblen's thought on capital in four points:

> 1) The industrial system of production has always been first and foremost the accumulation of the immaterial stock of technological knowledge, know-how and practices shared by a community. Production goods are only the material means to put this immaterial stock to use. Technological proficiency and productivity is determined culturally by the community, it is not the simple result of labor and tools.
>
> 2) The value of an asset, tangible or not, is the capitalized value of its earning-capacity for its owner, not of its individual productivity.
>
> 3) Tangible assets are normally serviceable to the community, but their earning-capacity is determined according to the extent of control over the community conferred upon the owners of the material means to put to use the community's technology. Tangible assets capitalize differential advantages in the sphere of production.
>
> 4) Intangible assets are normally non-serviceable to the community and capitalize differential advantages, such as institutional structures, conventions, legal rules, habits of thought, or *goodwill*; that confer any monopolistic capacity upon business concerns. Intangible assets capitalize differential advantages in the sphere of distribution.

Nevertheless, the capitalization of both tangible and intangible assets rest upon an immaterial factor, which is the extent of control over the community that the asset secures, be it in the sphere of production or distribution. If this control can be direct, for example

through the massive resort to advertising to manipulate the desires and habits of the common man, this control is first and foremost structural, and rests on established social structures and habits of thought. The contemporary example of Microsoft illustrates this point: Microsoft's high market value depends not on its productivity but on its capacity to restrain others' production. This capacity is not based on direct power to compel the population to act a certain way; instead, it is based on the fact that the community accepts the legitimacy of intellectual property, without which Microsoft's market value would collapse.

As Nitzan (1998) and Bichler and Nitzan (2000) have argued before, for Veblen, the accumulation of capital is not the accumulation of means of production, but, instead, an accumulation of control over the industry and the community. The notion of control, and its corollary notion of power, is intrinsically linked to the concept of capital. While Veblen proposes a very simple definition of capital (1904, 131): "'Capital' means 'capitalized putative earning-capacity', expressed in terms of value," this definition opens a door for an economic analysis in terms of control and power. In fact, for Veblen, capitalization is the subjective measure by the business community of the pecuniary control of a business enterprise over the community (2002 [1919a], 78-79):

> Such a consolidation of ownership and control on a large scale appears to be, in effect, a combination of forces against the rest of the community […] The new state of things brought about by such a consolidation is capitalised as a permanent source of free income. And if it proves to be a sound business proposition the new capitalization will measure the increase of income that goes to its promoter or to the corporation in whose name the move has been made.

For example, as a form of control over the community, the state and nationalism are important sources of intangible assets for corporations since, in the name of the national

interest, the state implements policies serving the national business interests (Sweezy 1958, 188-192). In his later work, Veblen's judgment about the role of the state leaves no ambiguity (1997 [1923], 36-37): "The constitutive authorities of this democratic commonwealth come, in effect, to constitute a Soviet of Businessmen's delegates, whose dutiful privileges it is to safeguard and enlarge the special advantages of the country's absentee owners". In this way, stronger states will allow stronger earning-capacity for national firms (Veblen 2002 [1919a], 92) since they are able to mobilize more political and military power to serve the firms' interests. In that sense, Veblen is a neo-mercantilist thinker; he refuses any conception of a "market economy" based on free competition. Instead, the organization of the economy has to be understood as the design of dominant interests shaping the knowledge structure according to their own interests. The idea of a modern market economy becomes elusive since the institutional development of intangible assets by business interests through the development of the predatory power of ownership rather produces a system of pecuniary feudalism (Veblen 1996 [1904], 176).

Capital does not need to be serviceable; it represents any earning capacity, whatever its origin. The usufruct produced by the industrial system is distributed according to differential advantages due to the ownership of tangible assets and intangible assets. Thus, not only are productive assets capitalized, but any institutional reality is capitalized as well, be it social, legal, political, cultural, psychological, religious, technical, or anything else that can grant an earning capacity. Capitalization is, therefore, based not only on control over productivity, but also on any institutional and structural power that confers control over the knowledge structure, and the community in general, in order to increase differential gains in the sphere of distribution or, in the words of Veblen, any capacity for vested interests to gain something

for nothing. In the case of particular economic sectors, like in the case of pharmaceuticals, we could say that capitalization of the firms is based on their control over relevant knowledge structure.

From the institutionalist Veblenian perspective, it is thus impossible to confine the concept of capital to the economic sphere. To the contrary, capital is at the core of every social sphere, or, one should rather say, it mobilizes every social sphere so as to achieve differential gains. Capital is not an industrial reality; it is a pecuniary practice that meddles with the whole reality of the community. It infiltrates the knowledge structure in every interstice to obtain differential earning-capacities. By defining capital as capitalized putative earning capacity without reference to productivity, Veblen can thus integrate power — any institutional form of power — in the economy. From such a perspective, political economy should examine capital accumulation by focusing on the dynamics of power and control over the knowledge structure and the community in general; thus gaining greater insight on the real dynamics of capitalism.

While Veblen emphasized the increasing control of businessmen over the "common man", he provided few analytical tools, however, to analyze inter-capitalist competition among businessmen. Instead, he mostly considers businessmen to be a homogeneous class (the "leisure class," "vested interests", "One Big Union of Interests" or "kept classes"), working as a group to consolidate its power to serve its interests. If coalitions and alliances between business enterprises are frequent, one should admit that strong competition and rivalry for world market shares also exist between businessmen. If Veblen offers great insight into the workings of corporate capitalism, he does not necessarily provide a framework that could serve more specific investigations into the dynamics of particular

capitalist sectors. The works of Bichler and Nitzan on differential accumulation, following Veblen's global understanding of the business world, provide a more complete and refined analytical framework to analyze the ongoing power struggles in the business world.

2.4 Bichler and Nitzan's Differential Accumulation

> "Ninety percent of the American people have little or no net worth.
> I create nothing; I own. We make the rules, Buddy, the news,
> war, peace, famine, upheaval; the cost of a paper clip.
> We pull the rabbit out of the hat while everybody else sits
> around their whole life wondering how we did it."
> - Gordon Gekko,
> *Wall Street* (Oliver Stone)

What was an implicit conclusion for Veblen is the explicit point of departure for Bichler and Nitzan: capital is social power. While Veblen embraced the idea that institutional power could be capitalized, Bichler and Nitzan go further, straightforwardly defining capital as power. For Bichler and Nitzan, capital is the social power that translates into earning-capacities for their owner. Capital is also something owned that can be exchanged, it is a commodity. Capitalization is thus the commodification of capitalist power in every dimension of the social structure.

Power, however, is never absolute: it is differential. The question is then how can we measure and analyze this power since it cannot be accounted in absolute terms but only in differential terms. Building on Veblen and Lewis Mumford (1967; 1970), but also on the works of Marx, Kalecki and Steindl, Bichler and Nitzan developed a power approach to

capital based on differential accumulation[19]. This theory provides an analytical framework where capitalization, which is the measure of putative gains, allows the mapping of the capitalist dimension of every social power.

For Bichler and Nitzan, as for Veblen, capital is not a productive asset. Capital is the social power over the rest of society, so as to engross earnings. This power cannot only be exercised through the ownership of the means of production, but also more broadly through the whole spectrum of social power. What firms capitalize (as going-concerns) is any stable earning-capacity. Thus, capital, in its pecuniary form, is not to be analyzed as a productive input but, instead, as crystallized power over the complex societal process of production and reproduction. Capitalism is thus analyzed as a whole social order, in which accumulation is not an offshoot of production, but, instead, the manifestation of a struggle over the shaping of the social process between dominant groups and the rest of society, as well as between those groups themselves (Bichler & Nitzan 2009). In this latter struggle, power is both the ends and means to accumulation. The theoretical analysis of this struggle between dominant groups is an important missing piece to Veblen's capital theory for understanding capitalist competition.

Bichler and Nitzan concentrate their analysis on corporate capitalism from the end of the nineteenth century, and examine the institutional settings of the capitalist struggle for differential gains. The authors argue that corporations, ruled by absentee owners, became dominant, not because they were more productive, but because they allowed greater control over large-scale industrial production, preventing it from becoming "excessively" productive (Bichler & Nitzan 2009), thereby ensuring greater profits. For this reason, they consider that

[19] See Bichler & Nitzan (2000; 2002b; 2004; 2009) and Nitzan (1998; 2001).

the analysis of capitalism has to focus on the most powerful corporations at the centre of capital accumulation. Following Veblen, capital is defined in terms of power over the social process, and capitalist power can be here quantitatively determined as the present value of anticipated flows of profit, expressed in monetary terms. The capitalization of dominant corporations becomes the quantitative index of their capitalist power over the social process.

Capital accumulation should thus be considered as an accumulation of power over the social process and can be quantitatively determined as the accumulation of claims over the future flow of profit. Capital accumulation, however, cannot be measured in material terms (an accumulation of means of production) or in absolute terms (accumulation of profits). The power of businessmen is the power to control part of the social process, and to measure power in a significant way it is necessary to measure it as compared to the power of others. Capital accumulation thus needs to be measured by bearing in mind the differential nature of power.

The pace of accumulation thus depends on two factors (Nitzan 1998, 204): 1) the institutional arrangements affecting profit expectations and 2) the normal rate of return used to discount them into their present value. In fact, capitalists always compare their capitalization as compared with others: "*The power of capitalists — at least in their own mind — is gauged relative to other capitalists*" (Nitzan 1998, 205, italics in the original). Capitalists never intend to maximize capital accumulation in the absolute, but always relatively to others: they seek to "beat the average", defined as the normal rate of return or the opportunity cost of capital. Accumulation should be measured relatively by comparing a group's (or corporation's) combined capitalization to that of an average unit of capital. In this power struggle to accumulate, the rate of "differential accumulation" of a particular group is

given by the rate of growth of the group's capitalization less the rate of growth of the average capitalization. They aim at beating the normal rate of profit to obtain a higher growth in capitalization than to average.

This approach is totally consistent with businessmen' everyday practices. Laurent Batsch, for example, (2002, 74-76) reminds us that what businessmen call "value creation" is not profits or surplus value, but, instead, profits realized above the normal rate of return[27]. Any student in corporate finance knows that it is worth it to invest in a project only if its net present value (NPV) is above zero – that is, if the anticipated flow of profit of the investment is above the normal rate of return. A negative NPV does not mean negative profits; it means that the project is less profitable than the average. This idea of "value creation" in the language of businessmen is nothing new conceptually as compared to the NPV or to what economists call the opportunity cost of capital, but its importance in the language of businessmen reveals the substance of the recent evolutions in business management.

Only groups with a positive rate of differential accumulation are said to "accumulate". For Nitzan and Bichler, dominant groups are considered to be engines of accumulation and the analysis should thus focus on such business groups capturing a large share of the profit pie. Those dominant groups can be defined as "Dominant Capital" (Bichler & Nitzan 2002b, 68-69). "Dominant Capital" in the United States can be summarily identified as all firms listed in the Fortune 500, which identifies the 500 biggest U.S. firms in terms of revenues.

[27] Batsch provides an example (2002, 75): suppose one buys a going-concern for 100 on January first and that, "normally", its value should be 108 after one year, since it represents the rate of growth of value for competitors. Suppose that by December 31, with zero inflation, the value of the going-concern is 103. Did the going-concern created value? The answer should be yes since the going-concern gained 3. However, if it had been known that the going-concern would be worth only 103 by the end of the year, nobody would have accepted to buy it since we would have known that by investing our money elsewhere, we would have had a profit of 8 instead of 3. In this way, the value of the substandard going-concern went down: today's equivalent of a sum of 103 in one year is 95.4 (=103/1.08). Who would accept to pay 100 an asset that cost 95.4 on the market? To destroy value is not losing money, it is gaining less than others.

The revenues of the Fortune 500 represent around 75% of the U.S. GDP. World "dominant capital" can be summarily identified as the firms appearing in the Global 500 that identify the 500 biggest global firms, which global revenues in 2007 represented more than a third of world GDP. For this dissertation, however, the term "dominant firms" will be preferred to "dominant capital" in order to sharply distinguish between firms, which are agents of the economy, and capital, which is defined as commodified power and not as an agent.

Bichler and Nitzan consider that all capitalist power in our society translates quantitatively in the sum of the net present value of all flow of income expressed in monetary terms. All capitalized income thus represents a huge pie over which capitalists fight to obtain a greater chunk. Accumulation translates into an increase in the relative part of the pie captured by a capitalist. Whatever the size of the pie, the struggle among capitalists is the struggle for a share of it, not for the growth of its absolute size.

Note that, from those premises, there is some ambiguity in the presentation of capital as power by Bichler and Nitzan. The authors sometimes define capital as power in general instead of only capitalist power, which would be power that translates into an earning-capacity. It is, however, essential not to include in the concept of "capital" forms of power that do not translate into a flow of income, such as the power of a mother over her child. Those are not forms of power related to capitalism; it is not part of an analysis of the capitalist system. However, any form of power that can translate into a stable flow of income for capitalists, or that can affect a stable flow of income captured by capitalists must necessarily be included in an analysis of the capitalist system. In a nutshell, capital must be defined as capitalized power that can translate into income or, in the words of Veblen, capitalized earning-capacity.

Capital accumulation has to be understood in differential terms, under which profitability must be measured relative to the profitability of an average firm. Bichler and Nitzan break down overall profitability as the product of employment (breadth) and profit per employee (depth). Note that one can break down profitability in other ways and, in this dissertation, profitability will be broken down between assets (breadth) and mark-ups (depth) since it is more relevant for the pharmaceutical business. Breadth and depth, according to Bichler and Nitzan (2002b, 49-72), can be subdivided into "internal" and "external" sub-routes, which can be considered regimes of differential accumulation:

> 1- External breadth translates in *greenfield investment* from which a firm can achieve differential accumulation by building new capacity and hiring new employees faster than the average. It is "external" since it causes a growth in production and employees, and a growth of the profit pie.
>
> 2- Internal breadth translates in buying competitors to increase market shares, which is usually made by *mergers and acquisitions*. It is "internal" since it does not entail the addition of anything new; it simply redistributes control over existing productive capacity.
>
> 3- Internal depth translates into *cost-cutting*, cheapening production costs faster than the average. It is "internal" since it redistributes income shares within the firm without consequences on the outside, like a change in prices.
>
> 4- External depth translates into *stagflation* where less is produced, but at higher prices. Dominant capital normally benefits from stagflation since the increase in prices outweighs the reduction in volume. In a stagflation regime, income is usually redistributed in favor of dominant capital since smaller firms lack political leverage[28]. It is referred to as "external" since the redistribution occurs through a change in the size of the pie.

[28] Bichler and Nitzan develop at length the mechanisms and consequences of stagflation since it is a central piece of their analysis of the oil and weapon industry and the politics of the Middle East. While this analysis of stagflation is groundbreaking in many aspects, it also resembles, in many ways, Hilferding's (1970 [1910], chap. XX) theory of economic crisis to benefit finance capital.

A regime prevails according to the context and strategies deployed by dominant firms. The main question is not how profits grow constantly in the absolute but how much they grow compared to others. In this way, a period of stagflation can be a period of important positive differential accumulation, for example for oil companies at the time of the oil crisis in 1973.

Bichler and Nitzan do not analyze capitalism in the same way than the Marxist tradition, which puts the emphasis on the social relation between the worker and the owner of the means of production. Instead, differential accumulation analyzes "business capitalism", focusing on the power that dominant corporations exert over the knowledge structure and the community in general. Dominant groups and corporations shape the life process of the community, gaining power that translates into higher revenues or lower costs. This approach is not inconsistent with the Marxist tradition, however, but offers a complementary understanding of the workings of capitalist economies by focusing on all dimensions of business power.

Differential accumulation is thus a conceptual framework of power accumulation between dominant business groups, in which differential capitalization is seen as the quantitative manifestation of qualitative power and allows one to examine power struggles between different capitalist groups. Note that, with the framework of differential accumulation, Bichler and Nitzan provide a general theory of capitalism, which they consider to be the only way possible to analyze the workings of the capitalist system. This dissertation does not enter into such theoretical debates. It simply considers that the framework of

differential accumulation provides important analytical tools to understand the evolution of capitalist power, defined as earning-capacities, in a specific business sector without falling back in the trap of the productivity doctrine of capital. By resorting to the conceptual framework of differential accumulation, one can measure quantitatively the relative power of dominant groups by measuring their differential profit-capacity. This framework allows one to infer capitalization, not only by observing social relations, but also by measuring the consequences of the process of differential accumulation in order to better identify its causes (Bichler & Nitzan 2009). In this dissertation, the quantitative evolution of the power struggle in the pharmaceutical business will be analyzed in order to understand the qualitative causes of this evolution.

Measuring Differential Accumulation

The analytical framework of differential accumulation brings with it some problems, the first of which is the access to the historical data for measurement, as for example the data on market value (for all outstanding equity and debt) to measure capitalization over time. For example, there exists no usable data on the capitalization of global firms prior to 1993, since historical data for market value are often unavailable. Moreover, as Bichler and Nitzan (2002b, 42) remark, market value can also be contaminated by investors' "hype"[29]. To measure differential accumulation, Bichler and Nitzan use, instead, the book value of the assets of firms as related in financial statements. Such a substitute, however, is imperfect. Capitalization is forward-looking: it is the actual value of its anticipated future earnings. It is

[29] This "hype" corresponds to what Keynes (1936, 161-2) called the "animal spirits", which are "the characteristic of human nature that a large proportion of our positive activities depend on spontaneous optimism rather than mathematical expectations, whether moral or hedonistic or economic".

based on what Commons (1934, 390-648) calls "futurity", namely the anticipated future according to which agents decide their present actions. Book values of assets are, as Bichler and Nitzan (2002b, 42) admit, a lagging indicator for capitalization, reflecting earning expectations prevailing when the assets were first recorded. Nevertheless, since the purpose is to measure relative and not absolute values, the measure of differential assets, over the long term, remains a very good index for differential accumulation.

By analyzing the differential accumulation of assets between 1954 and 1993, Bichler and Nitzan (2002b, 42-3) measure differential accumulation of dominant firms in the United States (firms listed in the Fortune 500) as compared with all mining and manufacturing firms and with all corporations. Their results are unambiguous (Table 2.1).

Table 2.1: Bichler and Nitzan's Analysis of Asset Accumulation in the U.S.
Comparison of the accumulation of assets between firms in the Fortune 500, all mining and manufacturing firms and all corporations (1954-1993)

	Average Assets in 1954 ($ million)	Average Assets in 1993 ($ million)	% Growth 1954-1993
Fortune 500	274	4740	1730%
Mining and Manufacturing	1.5	13	867%
All Corporations	1.1	5.5	500%

Sources used by Bichler and Nitzan: Fortune, U.S. Internal Revenue Service.

Dominant firms, appearing in the Fortune 500, achieve a rate of asset accumulation much more considerable than other corporations. When compared to all corporations, the differential accumulation of assets by dominant firms has been on average 3.8% per annum and 2% per annum when compared to all mining and manufacturing firms. In other words, dominant firms accumulated assets at a rate 3.8% faster than the average rate of asset accumulation for all firms and at a rate 2% faster than the average rate of asset accumulation for all mining and manufacturing firms. From this perspective, it becomes important to focus on dominant firms to understand the dynamics of accumulation, instead of analyzing "the economy" or "the market" as a whole.

2.5 Dominant Pharmaceutical Firms

"We are in the business to make money, not steel."
- David Roderick
U.S. Steel CEO

While there is no accepted and definitive list of the entities that embody dominant pharmaceutical firms, it is standard to consider that this sector is dominated by a group of firms, usually referred to as "Big Pharma". For Veblen, dominant firms are those with goodwill or intangible assets, of which monopolistic capacities form the bulk of their capitalization. The question is thus how to interpret this domination through intangible assets for pharmaceutical firms in the twentieth and twenty-first centuries. The conceptual toolbox

provided by Alfred D. Chandler, while requiring caution, is useful to identify the nature of this domination.

Chandler's Toolbox

To discuss the existence of dominant firms is to assume that some firms succeed better than others, that they are more "efficient" than others. This notion of "efficiency", however, needs to be developed. In the mainstream economic traditions, following Max Weber's discussion of markets as the embodiment of rationalization and efficiency (Weber 1978), the rise of corporate capitalism at the end of the nineteenth century, especially in the United Sates, is considered to be the result of corporate organizations' greater productivity as compared with other forms of institutional organization. For neo-institutional economists, for example, the corporations thus exist because they are more productive than the constant recourse to market transactions that would involve greater transaction costs (Williamson 1981; North 1981). For many, it is the business historian Alfred D. Chandler (1977; 1990) who represents perfectly the "efficiency theory". According to Chandler, business corporations arose because they were more efficient in organizing large-scale production due to economies of scale and scope. Some business historians, however, like Roy (1997) or Lamoreaux (1985), presented convincing econometric rejections of Chandler's contention that corporations brought greater industrial productivity, by showing that the rise of corporate capitalism was, instead, the result of power struggles to control and restrain industrial productivity for the benefit of private interests. Chandler's analysis can nevertheless be very useful in identifying Big Pharma in spite of its constant recourse to the "efficiency logic". It allows us to understand why a corporation survives or not. "Efficiency", however, should not

be understood here in terms of industrial productivity (output in relation to input), but, instead, in terms of profitability (income related to outlays).[30] The works of Chandler are sometimes ambiguous on this point, since they remain entangled in the confusion between output and income, which is central to the productivity doctrine. In his earlier works, Chandler (1977) clearly considered efficiency in terms of output, but in his recent works devoted to the pharmaceutical business (2005), efficiency is understood, instead, in terms of income. For example, Chandler considers that firms' functional capabilities that are product-related not only include product development and manufacturing, but also include marketing and promotion to obtain higher prices. Efficiency is not defined in industrial terms anymore, but, instead, in terms of business profitability.

In his two books, *Inventing the Electronic Century* (2001, 1-12) and *Shaping the Industrial Century* (2005, 3-18), Alfred D. Chandler provides a conceptual approach that allows us to interpret the structure for the domination of a sector. Chandler's basic idea is that the competitive strength of industrial firms in market economies rests on *learned organizational capabilities* (Chandler 2005, 6):

> The capabilities are product-related in terms of technologies used and markets served. These product-related capabilities, moreover, are learned and embodied in an organizational setting: individuals come and go, but the organization remains. Thus, in modern industrial economies, the large enterprise performs its critical role in the evolution of industries not merely as a unit carrying out transactions on the basis of flows of information, but, more important, as a creator and repository of product-related embedded organizational knowledge.

Those organizational capabilities include three types of capability: 1) technical knowledge required for the R in R&D; 2) functional capabilities that are product-related

[30] On the distinction between output and income, see John R. Commons (1934, 254-301).

(development, manufacturing and marketing) and 3) managerial capabilities. Only firms "efficient" enough (in business terms) in building their organizational capabilities can become core companies of a sector.

In a new industrial sector, the *first movers* are the first enterprises to develop an integrated set of capabilities essential to commercialize the new products in volume for national or world markets. They benefit from their integrated capabilities, which become their *learning bases* to develop their control of the networks of production and distribution, to improve existing products and processes, or to adapt to new conditions, such as those of war or depression. This way, the *first movers*, and those who in some way managed to catch up for their late arrival in the industry, become *core companies*, or dominant firms, that set the direction in which the whole industry evolves (Chandler 2005, 9):

> The concentrated power of technical, often proprietary, and functional knowledge embedded in the first movers' integrated learning bases is such that a relatively small number of enterprises define the evolving paths of learning in which the products of new technical knowledge are commercialized for widespread public consumption. The barriers to entry thus prevent startups from creating effective integrated learning bases essential to compete in the industry.

Due to their needs for means of production, raw material, research specialists, distributors, advertisers or financial services, the core companies do not embody the entire sector by themselves. A business sector is made of the core companies along with a *supporting nexus* of concatenated and complementary, rather than competitive, enterprises. The supporting nexus is made of small, medium or large firms that cooperate with core companies; but rarely do core companies emerge from this nexus (Chandler 2005, 8). The main competitors to national core companies are usually foreign core companies or core

companies in other sectors with similar capabilities in terms of technology, manufacturing, and marketing. Note that dominant pharmaceutical firms appeared mostly in the nineteenth century and that since the 1920s no new firm has been able to join the select group of pharmaceutical core companies, except for Amgen in the late twentieth century[31].

Identifying Big Pharma

Listing the most important global pharmaceutical firms in terms of capitalization and revenues can be helpful to identify core companies or dominant firms that constitute Big Pharma. On an annual basis, the first 500 global firms are listed by their importance in terms of revenues (Fortune Global 500) and by their importance in terms of capitalization (Financial Times Global 500). The pharmaceutical firms appearing in both lists appear in Table 2.2. Since the rates of profit are very high in the GPB, it is thus normal that more firms appear in the list in terms of market capitalization.

[31] On how Amgen managed to become part of Big Pharma by capturing the public research on EPO, see Goozner (2004, 13-38).

Table 2.2: Pharmaceutical Firms Listed in the Fortune Global 500 and in the FT Global 500 in 2006

Company	Country	FT Global 500 Rank	Capitalization (Billion $)	Fortune Global 500 Rank	Revenues (Billion $)
Pfizer	US	13	183.4	101	51.3
Johnson and Johnson	US	14	176.2	104	50.5
GlaxoSmithKline	UK	19	151.9	143	37.8
Novartis	Switzerland	21	146	177	32.2
Roche	Switzerland	25	130.6	204	27.3
Sanofi-Aventis	France	28	128.6	159	33.1
Genentech	US	51	89.1	—	6.6
Amgen	US	56	86.2	—	12.4
AstraZeneca	UK	62	79.4	253	24
Merck	US	65	77	289	22
Abbott Laboratories	US	88	65.3	283	22.3
Wyeth	US	89	65.2	343	18.8
Eli Lilly	US	95	62.5	464	14.6
Takeda Pharmaceutical	Japan	130	50.6	—	9.6
Bristol-Myers-Squibb	US	138	48.2	321	19.2
Teva Pharmaceutical	Israel	216	32	—	5.3
Bayer*	Germany	233	29.2	163	34
Gilead Sciences	US	239	28.8	—	2
Schering Plough	US	246	28.1	—	9.5
Astellas Pharma	Japan	340	21.7	—	3.8
Schering	Germany	378	20.1	—	6.4
Novo Nordisk	Denmark	405	18.7	—	5.5
Genzyme	US	447	17.5	—	2.7
Daiichi Sankyo	Japan	467	16.7	—	5
Biogen Idec	US	481	16.2	—	2.4

*: Bayer is usually classified as a chemical firm but its production in pharmaceuticals is important enough to include it in the list.

Sources: Fortune Global 500 2006; FT Global 500 2006

Since differential accumulation is based on the evolving earning-capacities of the different firms, the list in terms of capitalization (actualized earning-capacity) is more relevant. The number of pharmaceutical firms appearing in the FT Global 500, however, is too high since it includes firms that are part of the supporting nexus of dominant firms. For the purpose of the analysis in terms of differential accumulation, a more refined selection has to be made of the firms that appear on the list of Big Pharma. The list should not include Teva Pharmaceutical, which produces generics and has interests far different from those of Big Pharma. The Japanese firms Astellas Pharma and Daiichi-Sankyo benefit from the well-protected Japanese pharmaceutical market, but their foreign sales are dependent upon their alliances with foreign firms. Among Japanese firms, only Takeda can be considered a core company since it built its own foreign sales and marketing capabilities in the U.S. and Europe[32]. Novo Nordisk, which produces approximately one third of the world's supply of insulin and half of the world's supply of industrial enzymes, may have found important niches in the supporting nexus (Derdak 1988, 658), but remains too small and too focused to be considered part of Big Pharma. The biotech firms Gilead Sciences and Biogen Idec are totally dependent on their alliances with core companies, while Genentech, Amgen and, more modestly, Genzyme can be considered to have developed an integrated learning base in biotech (Chandler 2005, 270-273). However, Genzyme remains too small to be considered a core company, and the majority of Genentech is owned by Roche. Only Amgen can be considered to be a new player among core companies, even if Wyeth owns 10% of its shares.

[32] Takeda has long been dependant on joint ventures with Big Pharma firms for selling its drugs abroad. Its evolution into a core company can be set in 1997 when Takeda decided not to renew its agreement with Abbott Laboratories, which was managing Takeda foreign sales through the joint venture TAP Pharmaceuticals (Chandler 2005, 200).

Bayer, a core company in chemicals that also produces pharmaceuticals since the nineteenth century, has been restructuring in 2006 by buying 95% of Schering, so as to focus more on pharmaceuticals. As for Schering-Plough, it has long been an important core company in pharmaceuticals, but it had many problems in recent years due to the 2002 expiration of its patent on its leading product Claritin, but also because of the many lawsuits against its marketing practices and a $500 million fine over protracted manufacturing problems (Derdak 2003, 356-62). In spite of these problems, Schering-Plough, a first-mover in biotech, retains strong integrated capabilities in R&D and maintains a strong marketing network. For all these reasons, Schering-Plough must still be considered as a dominant firm.

Thus, since the analysis focuses on capitalization, Big Pharma can be identified as the firms listed by the Fortune Global 500 plus the firms Genentech, Amgen, Schering-Plough and Takeda Pharmaceutical, since they all have an important capitalization and are not dependent on other core companies. They each have developed an integrated learning base, especially in terms of R&D and marketing capabilities. While the boundaries of Big Pharma are subject to change, it is considered that, in 2006, Big Pharma was constituted by seventeen firms, or sixteen if we consider that Genentech is controlled by Roche (Table 2.3).

Table 2.3: List of Big Pharma Companies for 2006

Company	Country	FT Global 500 Rank	Market Value (Billion $)	Revenues (Billion $)
1- Pfizer	US	13	183.4	51.3
2- Johnson and Johnson	US	14	176.2	50.5
3- GlaxoSmithKline	UK	19	151.9	37.8
4- Novartis	Switzerland	21	146	32.2
5- Roche	Switzerland	25	130.6	27.3
6- Sanofi-Aventis	France	28	128.6	33.1
7- Genentech	US	51	89.1	6.6
8- Amgen	US	56	86.2	12.4
9- AstraZeneca	UK	62	79.4	24
10- Merck	US	65	77	22
11- Abbott Laboratories	US	88	65.3	22.3
12- Wyeth	US	89	65.2	18.8
13- Eli Lilly	US	95	62.5	14.6
14- Takeda Pharmaceutical	Japan	130	50.6	9.6
15- Bristol-Myers-Squibb	US	138	48.2	19.2
16- Bayer	Germany	233	29.2	34
17- Schering Plough	US	246	28.1	9.5
Total	**-**	**-**	**1597.5**	**425.2**

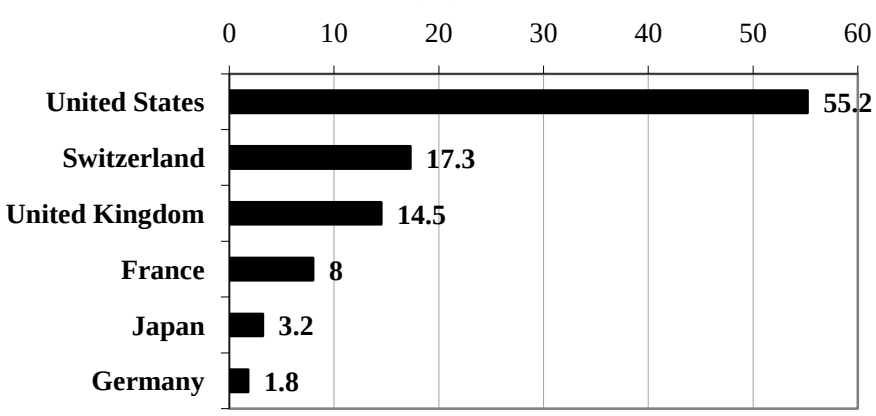
Sources: FT Global 500, Fortune Global 500

Those seventeen dominant firms in pharmaceuticals are the core companies of this business, and most of them were first movers in the sector as early as the nineteenth century. With their integrated learning bases, they are the primary engines for the continuing evolution of their business sector through commercializing products of new technologies

fostered by advances in science and engineering (Chandler 2005, 9). Those firms control almost two-thirds of the global market shares, in pharmaceuticals; in short, they control the knowledge structure in pharmaceuticals.

The dominant firms embodying Big Pharma are also very concentrated in terms of their country of origin, defined in terms of where the head office is located. Since the market value reflects the actualized value of anticipated earnings, the control over anticipated earnings, i.e. the capitalist power to engross incomes through the ownership of pharmaceutical enterprises, is mostly in the hands of American interests (Figure 2.4).

Figure 2.4: National Share of Global Capitalization for Big Pharma in 2006



Source: FT Global 500

This figure unambiguously portrays the supremacy of American firms in the GPB. This supremacy did not exist from the beginning; it was built slowly against European firms through the twentieth century. In fact, the history of the GPB (see Chapter 4) can be read as the history of how American firms managed to become dominant in a sector controlled by

foreign interests by developing their own intangible assets via beneficial American industrial policies.

2.6 Differential Accumulation in the Pharmaceutical Business

"If our Treasure were more than our Neighbouring Nations,
I did not care whether we had one fifth part
of the Treasure we now have."
- Roger Coke (1675)

The differential accumulation conceptual framework provides a general theory of capitalist power that can be used to analyze different business sectors, including the pharmaceutical business. It provides a measure of the differential earning-capacity of pharmaceutical firms and therefore an indication of their relative power. To analyze the nature of capital in the KBE, the quantitative measure of differential accumulation offers a solid ground to understand, in quantitative terms, its nature as a new dynamic of capital accumulation. The idea of analyzing the KBE as a whole, however, is questionable since not all business sectors embrace "knowledge capital" at the same pace. Besides, in the different sectors identified with the idea of a "New Economy", namely telecommunications, information technology and pharmaceuticals (including biotechnology), the qualitative story underpinning each sector is simply too different to argue in terms of a monolithic process common to all sectors. For the present analysis, the focus is limited to pharmaceuticals, which exemplifies a durable economic and structural transformation since the 1980s. The task remains to identify the importance and the nature of those economic transformations. In

order to provide the quantitative story of differential accumulation for pharmaceuticals, it is first necessary to measure the evolution of differential profits in this sector.

The proposed analysis of the pharmaceutical business is made with an eye to the possibility of an emerging KBE, in which knowledge-based firms would accumulate at a faster rate than other corporations. Because of the focus on Big Pharma, it is necessary to compare those firms with dominant firms in other sectors. Differential accumulation can be measured by comparing the absolute profits for an average dominant firm in pharmaceuticals as compared to profits for an average dominant firm in other sectors.

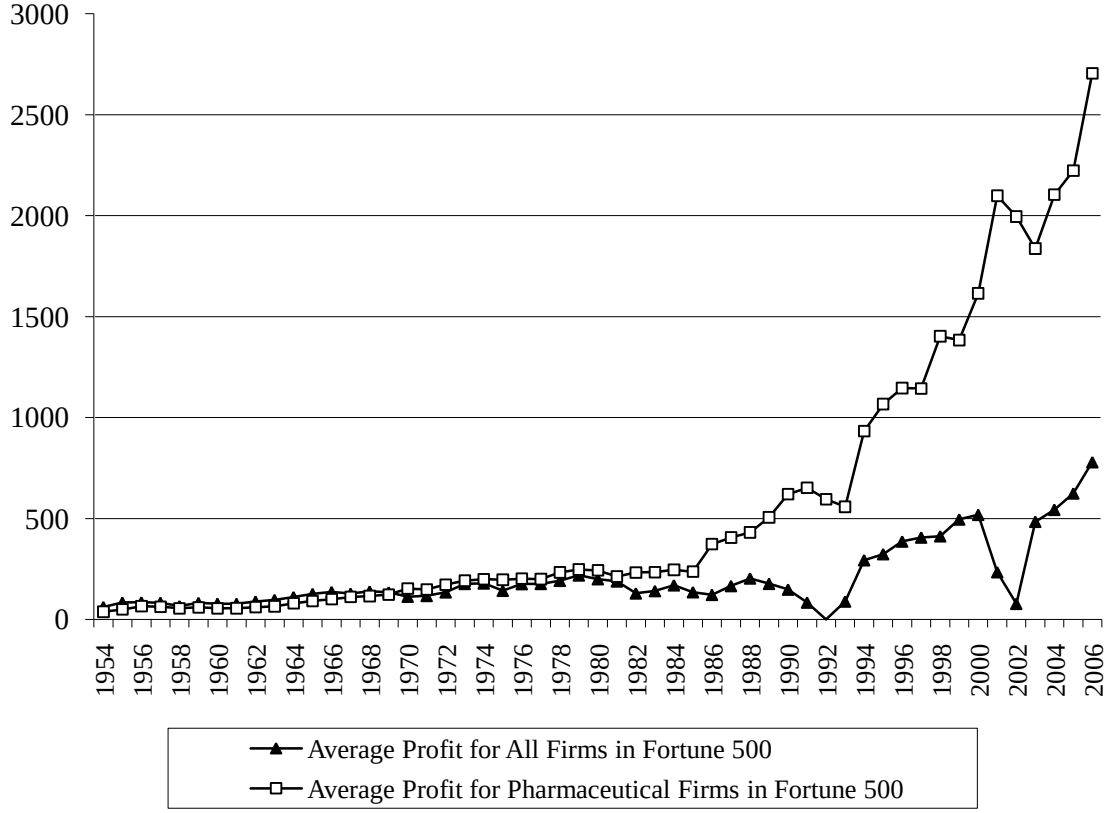
Profits, in the same way as book values, are a lagging indicator for capitalization, reflecting realized earnings instead of anticipated earnings. Such a standard eliminates investors "hype" from our calculations, and this point is important for pharmaceuticals due to the important hype caused by biotechnology. Profits are the direct result of the firms' earning-capacity, and since the purpose here is to measure relative and not absolute values, the measure of differential profits over the long term remains a very good index for differential accumulation.

A final problem remains: there is no workable historical data of profits for global firms. The only workable source that provides a good historical perspective is the Fortune 500 database, providing data on profits for the 500 most important firms in terms of revenues in the United States since 1954. By keeping in mind that the United States represents the main market for pharmaceuticals, national data for the United States provides good indication for global trends. Using the Fortune 500 database, it is possible compare the evolution of the earning-capacity of dominant pharmaceutical firms (the ones included in the Fortune 500)

and other dominant firms (see Figure 2.5). Details about the calculations are provided in Appendix A.

Figure 2.5: Big Pharma Differential Accumulation

Profits of an average U.S. dominant pharmaceutical firm as compared to an average Fortune 500 firm (1954-2006; in millions of constant 1984 US$)



Source: Fortune

For the purpose of this dissertation, the KBE is considered to be the increasing profitability of firms focused on sectors considered to involve an important capitalization of

knowledge. In quantitative terms, the KBE is the rising discrepancy in profits for knowledge-based firms. Figure 2.5 allows an understanding of the KBE in the case of pharmaceuticals as the rising differential profitability for dominant pharmaceutical firms as compared to other dominant firms. One can observe a surge in differential profitability for pharmaceutical firms since the beginning of the 1980s, which corresponds to the period during which the KBE is considered to emerge. The emergence of the KBE in this sector can thus be measured in quantitative terms, but a qualitative explanation of this rising discrepancy is absolutely necessary to complete the analysis. The rest of this dissertation aims at providing such qualitative explanation of the rising differential profits for Big Pharma.

Qualitative Outline: Big Pharma's Structural Competition

The core of capitalization of dominant corporations, or of dominant groups that own corporations, is their intangible assets, or, as defined earlier, their capacity to mobilize institutional social power in order to increase earnings. From such a point of view, competition between corporations takes the form of a struggle to influence and transform social structures, in order to mobilize social power and accrue differential earning-capacity. Analyzing the process of capital accumulation becomes the analysis of the evolution of the institutional structure providing earning-capacity to dominant firms.

In terms of method, an analysis in terms of differential accumulation entails a new understanding of the notion of competition among capitalists. In standard economic theory, competition is analyzed in terms of price competition or monopolistic competition. Competition between capitalists is considered either a market competition aiming at lowering prices to sell more, or a monopolistic competition based on product differentiation and mark-

up pricing. With differential accumulation, capitalist competition has to be understood as a series of power struggles in shaping the social structures, including norms, habits, legislations and social constraints, which translate into a greater differential flow of earnings. Competition becomes structural, that is, by transforming willingly the socio-economic institutional settings to increase strategic control over the industry and society by business interests. Dominant groups mobilize all their capacities and business network power to influence consumers, laws, policies, sense of nationhood, regulatory regimes in ways to modify the socio-economic structure so as to accrue their differential gains.

In the case of pharmaceuticals, as it will be shown, the capitalist power struggles for differential accumulation can be found, for example, in the struggles to implement new health standards, to create new products, to get greater tax credits, to extend patent protection, to create narratives legitimizing high profits, to produce sympathetic analysis of the industry, to advertise products to physicians and consumers, to educate medical doctors or to incite universities to patent their discoveries. The structural competition for differential accumulation is not just a struggle in the economic sphere; it is a series of local struggles mobilizing every power in every social and cultural sphere in order to increase capitalization.

To better understand the main power struggles and institutional causes behind this rising differential profitability in pharmaceuticals, the constituents of this differential profitability will be broken down in Chapters 5, 6 and 7 in terms of breadth and depth. This distinction allows an identification of what constitutes novelty in the "New Economy", by highlighting the structural changes in the pharmaceutical business in terms of its knowledge structures that made possible the steep increase in pharmaceutical companies' earning-capacity.

In the case of pharmaceuticals, the sub-routes of structural competition for breadth and depth can take different forms:

1- External breadth translates into greenfield investment under the form of gross fixed capital formation or R&D.

2- Internal breadth translates into mergers and acquisitions among pharmaceutical firms.

3- Internal depth through cost-cutting translates, for example, into restructuring, lay-offs, lower tax burden, outsourcing or public subsidies for R&D.

4- External depth through stagflation translates, for example, into extended intellectual property rights that increase price and reduce volume, marketing that favors high-price brand name drugs, deliberate regulations that allow higher prices for medicines or greater barriers to entry.

In subsequent chapters, each of those sub-routes will be explored to show their relative importance. Differential accumulation through structural competition is the cornerstone of corporate capitalism. The present analysis measures capitalist power and explains the historical foundation of this power for dominant groups in the case of pharmaceuticals. Ultimately, following Veblen's lead, the intention is to show that the profitability achieved in the KBE is not due to greater productivity, but, instead, to transformations in the knowledge structure, providing firms greater means to mobilize social power and greater capacity to control and even restrain productivity.

3. GLOBAL PHARMACEUTICAL BUSINESS: BIG MONEY, LITTLE INNOVATION

"Today's medicines finance tomorrow's miracles"
- GlaxoSmithKline's 2004 ad campaign

The Global Pharmaceutical Business (GPB) is not an easy business to understand. A series of debates currently rage over different issues related to this sector, embodying a range of conflicting narratives concerning the nature of its business model over the last fifty years. In the late 1950s, Senator Estes Kefauver, Democratic Chairman of the United States Senate's Anti-Trust and Monopoly Subcommittee, put together the first extensive indictment against the business workings of the pharmaceutical industry. He laid three charges at the door of the industry (Kefauver 1965, passim): 1) patents sustained predatory prices and excessive margins; 2) costs and prices were extravagantly increased by large expenditures in marketing; 3) most of the industry's new products were no more efficient than established drugs on the market. Kefauver's indictment against a marketing-driven industry created, for many, a representation far different than the industry's depiction of itself: the image of life-saving "researchers in white coats" now conflicted with one of greedy "reps in cars" (Froud et al. 2006).

While contemporary industrial lobbies, particularly PhRMA and R_X&D, contend that the rising cost of innovation necessitates greater profits in order to fund R&D, many critics contend that the GPB is, in fact, cashing in easy profits through massive marketing but contributing little to innovation. A serious investigation of the GPB is necessary to determine

the veracity of each claim. Specifically, before analyzing the causes of the increasing earning-capacity of the GPB, it is necessary to demonstrate that there is no such thing as a surge in pharmaceutical innovation that could explain the increasing profit of this knowledge-based sector. For example, it is necessary to investigate at length the claims of the industry that its pricing strategies are simply the result of their important expenditures in R&D because of the high costs to produce new drugs. The hypothesis defended in this chapter is that the increasing earning-capacity of the GPB is linked with an important decline in therapeutic innovation. Before explaining the causes of this decline, something that will be done in the next chapters, it is central here to measure the importance of this decline. For this sector, however, the difficulty for any analyst is that most data are 1) privately owned by market research companies; 2) impossible to verify; or 3) simply hidden. As such, this chapter addresses this difficulty, supplying a precise portrait of the workings of the sector, using the most accurate available data.

Given the concerns about the validity of industry-derived data, the chapter balances industry sources with critical examinations of the industry. It mainly draws on data provided by IMS, considered the authoritative source for pharmaceutical market intelligence, as well as the OECD Health Database. Those data are supplemented with annual reports of firms and industrial lobbies, such as PhRMA or EFPIA. However, these latter data can be inaccurate in different ways, and where data has been subject to criticisms, alternative sources are introduced for comparison.

To capture the parameters of today's GPB, it is necessary to identify not only its main economic components in terms of production and sales, but also some components of its knowledge structure, specifically, its segmentation (generics vs. brand-name; OTC vs. R_X;

etc.), and the nature of its R&D and innovation process (the pipeline and clinical trials), both in terms of costs and results. Here, the structural components of the industry are captured by identifying what is considered the dominant business model. After identifying the global structures in terms of sales, production and segmentation of the sector, this chapter analyzes the claims offered by the industry to link the high prices of their products with the increasing costs involved in the R&D process. Finally, it assesses, both quantitatively and qualitatively, the evolution of innovation in this sector.

3.1 Sales and Production in Pharmaceuticals

In 2005, according to IMS[33] (2006), the global pharmaceutical markets represented sales of $602 billion. It corresponds approximately to 1.4% of world GDP and to 4.4% of world industrial production[34]. North America, Europe and Japan accounts for 82.3% of global sales in pharmaceuticals (see Table 3.1). Sales have been increasing steeply in the last years; from 2000 to 2005 global sales increased by 74% in constant dollars. The global pharmaceutical market is divided into different therapy classes, and almost 30% of all global sales in pharmaceuticals are made in ten therapy classes, according to the official ATC classification (Table 3.2).

[33] IMS is the most important data source on pharmaceuticals covering 70 audited countries that represent around 94% of world sales. For audited countries (markets) IMS monitors and records every transaction. IMS audited $565.9 billion in pharmaceutical sales in 2005 and thus estimated that total global sales were $602 billion if we include unaudited markets.
[34] Calculations based on IMS and the CIA World Factbook 2006.

Table 3.1: Global Sales in Pharmaceuticals and Growth by Region in 2005

World Audited Market	2005 Sales (billion $)	% Global sales	% Growth 2000-2005 (constant $)
North America	265.7	44.1	+ 71
Europe	169.5	28.2	+ 111.9
Japan	60.3	10	+ 31.8
Asia, Africa and Australia	46.4	7.7	+ 81.3
Latin America	24.0	4	+ 28.3
Non-Audited (estimation)	36.1	6	—
World	602	100	+ 74

Source: IMS

Table 3.2: **Leading Therapy Classes by Global Sales in 2005**
(Excluding unaudited markets)

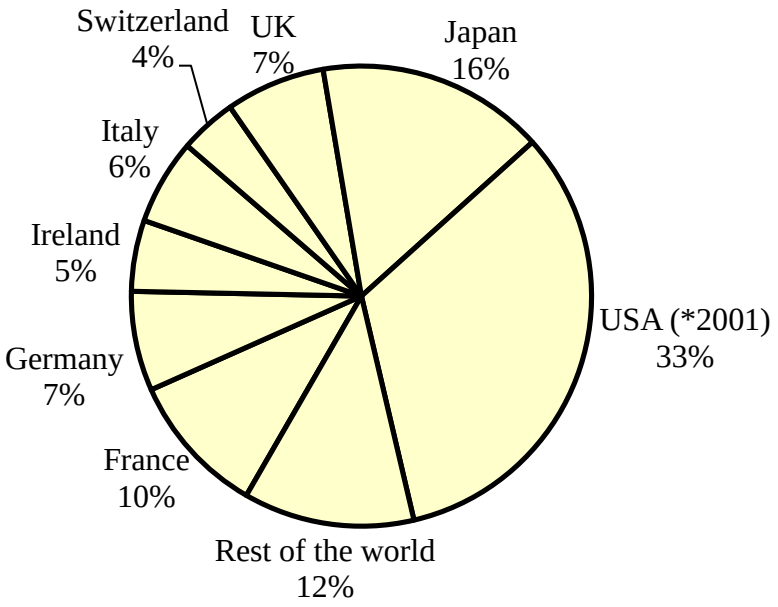
World ATC Therapy Class Sales	2005 Sales (billion $)	% World Sales
Cholesterol & triglyceride reducers	32.6	5.8
Anti-ulcerants	26.9	4.8
Antidepressants	19.9	3.5
Antipsychotics	16.3	2.9
Erythropoietins	12.4	2.2
Calcium antagonists, plain	12.0	2.1
Anti-epileptics	11.7	2.1
All other antineoplastics	11.5	2.0
Oral antidiabetics	10.8	1.9
Platelet aggregation inhibitors	9.8	1.7

Source: IMS

Production is largely dominated by Europe, Japan and North America (the U.S.A. and Canada) who together produce around 90% of all pharmaceuticals. While the United States

represents by far the biggest market for pharmaceuticals, with 42% of world sales[35], they produce less than a third of all pharmaceuticals (Figure 3.1).

Figure 3.1: World Production of Pharmaceuticals in 2003



Sources: VFA, OECD, EFPIA

The discrepancy between sales and production for the United States can be explained by the fact that the United States is a net importer in terms of drug volume, and also by the fact that drug prices are higher in the United States, so that the accounted price of an imported drug unit is higher than the accounted price of an exported drug unit. Brand-name drugs

[35] Share of U.S. world sales in pharmaceuticals for MAT September 2005 (IMS Health Canada 2006).

prices in the United States are approximately 50% to 100% more expensive than in Canada or Europe (Table 3.3). Note that drug prices, however, are usually more expensive in developing countries that lack production facilities for pharmaceuticals than in developed countries that have manufacturing facilities for pharmaceuticals (WHO & HAI 2003; Cameron et al. 2009).

Table 3.3: Average Foreign to American Price Ratios for Patented Drugs in 2007

	U.S.	Canada	France	Germany	Italy	Sweden	Switzerland	U.K.
% of U.S. price	100	60.9	51.8	59.6	47	57.3	60.4	59.8

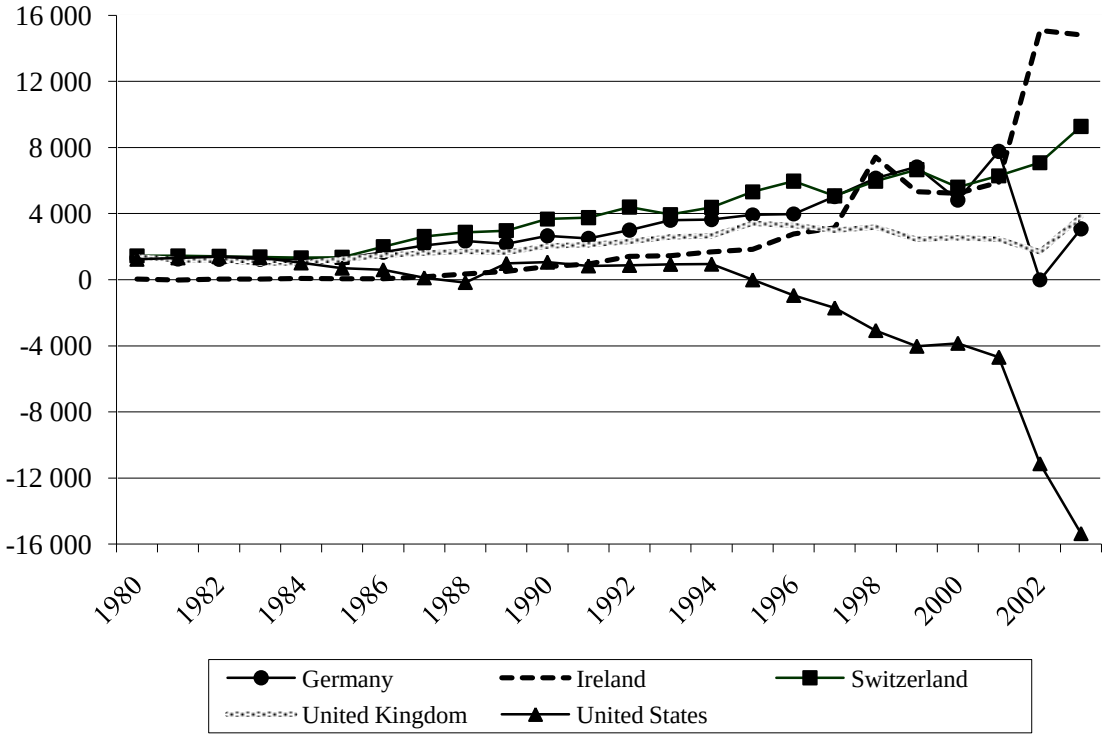
Source: PMPRB Annual Report 2007

While the United States is the world's largest drug producer, it is also the world's largest drug consumer. The United States is in fact the main net importer of drugs, while Ireland is the main net exporter (Figure 3.2). Other important net importers of drugs in 2003, not shown on the figure, were Canada ($4.1 billion), Spain ($3.9 billion) and Japan ($3 billion). Note that most emerging countries, such as Brazil and South Korea, still remain net importers of drugs, rare exceptions being India and China with trade surplus in pharmaceuticals of less than $1 billion each[36].

[36] Calculations for industrialized countries based on OECD Health data and Japan's Ministry of Finance, calculations for emerging countries based on UNIDO Industrial Statistics Database.

Figure 3.2: Trade Balance in Pharmaceuticals 1980-2003

Million $ (Current Price at Exchange Rate)



Source: OECD Health Data

Available statistics seem to belie the age-old concept of trade balance. Since its creation by Misselden (1623), the trade balance concept has been used to measure nations' economic power. For modern neorealists studying international political economy (IPE), as for 17th Century mercantilists, the trade balance remains an important indicator of national economic power, since the trade balance reflects the competitiveness of the national economy. Under such an approach, the competition for power is a game between states, which organize their economic policies in ways that maximize their national power. Hence, the United States should be fighting to reduce its trade deficit in pharmaceuticals by reducing drug prices. Yet,

as discussed above, U.S. drug prices remain higher than elsewhere. An answer to this conundrum is revealed if we take into account the transnational nature of the GPB.

3.2 The Transnational Nature of the GPB

A country-based global outlook on pharmaceutical production and trade, which is usually favored by most neorealist analysts of the global economy, is misleading. From the neorealist point of view, states and their national interests are the keys to understanding the world economy[37]. From this perspective, one could assume that the national interest of the United States should be to encourage worldwide price reductions in pharmaceuticals in order to lower the U.S. trade deficit, which has been an important Achilles' heel of U.S. international power in recent years (Vanel 2006). The United States, however, remains the main advocate of extending IPR worldwide, especially the IPR clauses concerning pharmaceuticals, for example by promoting a TRIPs+ approach[38] to increase minimum standards for patents and to reduce parallel imports[39]. This strategy can only increase

[37] See for example Gilpin (2001) or Keohane (1986). For those neorealist authors, the IPE is essentially the arena where self-interested states confront each other using all their sources of power. Cooperation is possible if it is rational for states to cooperate. The debate thus turns on how to create rules of governance in international organizations that will allow cooperation between States in an international regime.

[38] The TRIPS+ approach is associated with the American and Swiss strategy at the WTO that considers that the TRIPS Agreement ratified in 1995 should not be interpreted as an end result but as a basis to continue to extend IPR standards worldwide. The TRIPS+ approach results in a very narrow interpretation of the TRIPS Agreement in an auspicious way for IPR owners.

[39] A parallel import, also known as "grey product", is a product sold legally at a cheaper price in a country and exported to another country without the permission of the owner of the IPR on the product in the second country, reducing mark-ups for the product. Parallel imports are usually the import of legal generics but can also be the import of a brand-name product sold at a cheaper price in a different country. Drug manufacturers sell their products at highly differentiated prices in different countries, with variations in retail prices ranging around 5900% for brand-name products (Bala and Sagoo 2000) and 6000% for lowest-priced generics (Cameron et al. 2009); parallel imports are thus not exceptional. Parallel imports in the pharmacy market were 5% in 2004 (VFA 2005, 50). The debates over parallel imports under TRIPs are summarized in Gagnon (2003).

furthermore the price of drug imports to the United States. Also, since Ireland produces 5% of world pharmaceuticals and is the main net exporter of medicines, a neorealist point of view would consider Ireland to be a powerful player in the global pharmaceutical market, and would expect Ireland to defend stronger IPR in foreign countries, which is not the case. Instead, the TRIPS+ approach is defended by the United States and Switzerland (see Gagnon 2003). Ireland is an important producer of pharmaceuticals because it provides research-based TNCs a great point of entry to the European Union; as an English-speaking country using the Euro, Ireland offers Europe's lowest tax-rate on profits (12.5%) and an important tax credit (20%) on R&D (Associated Press 2006). Ireland, however, is not considered to be a proponent of IPR extension in world trade forae, as compared to the United States, Japan or Switzerland. The geographical location of the industry thus does not seem a primary factor for understanding a country's position on IPR in pharmaceuticals.

The GPB cannot be properly analyzed from such a neorealist point of view for two reasons:

> 1) States that favor economic growth and job creation are subjected to what could be called the structural power of global capital (Gill and Law 1989). To attract investments, national governments are constrained to offer a set of regulations that will allow increased returns on investments on their national territory. Without such regulations in the interests of capital owners, investments would flee the country. Ultimately, it is the power of capital that organizes economic, political and social structures, not states.

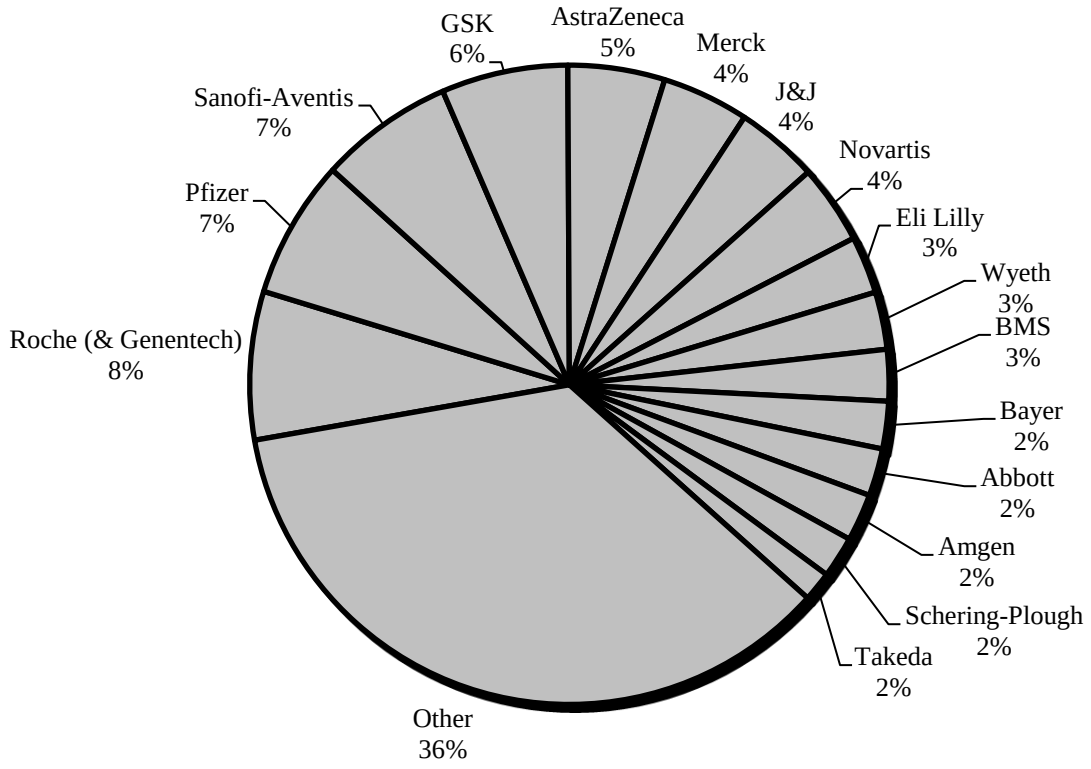
> 2) Dominant groups behind the manufacturing of pharmaceuticals are transnational corporations i.e., corporations that have a country of origin but operate on a global scale. International alliances between firms, mergers and acquisitions, outsourcing and intra-trade firms are the normal strategies for transnational corporations and those practices blur national boundaries.

There is no Irish pharmaceutical industry as such or American pharmaceutical industry as such. Instead, there are dominant pharmaceutical groups, mostly originating in the United States and operating on the global scale. They can shift production or the value of sales from the United States to Puerto Rico or India or Ireland or to wherever is advantageous for their pecuniary interests. For example, the American-based pharmaceutical company Eli Lilly lists R&D facilities in Australia, Belgium, Canada, England, Germany, Japan, Singapore, Spain and the United States; and lists manufacturing facilities in Brazil, China, Egypt, France, Germany, Ireland, Italy, Japan, Korea, Mexico, Pakistan, Puerto Rico, Spain, the United Kingdom and the United States; and conducts clinical research in more than 50 countries around the world[40]. In spite of its geographical diversification, Eli Lilly has 66% of its long-lived assets in the United States, employs more than half of its workforce in the United States, and realizes 53% of its sales in the United States[41], where prices are higher than in other industrialized countries, and where tax breaks on R&D are generous. Taxes on profits, however, are higher in the United States than in other countries and Eli Lilly reported for 2004 only $200 million in pre-tax profits from United States compared with $2,800 million in profits in the rest of the world. Eli Lilly thus paid in 2004 only $37 million in state and federal taxes in the United States, which represents 1.3% of its worldwide pretax profits. One can assume, however, that most of its profits were made in the United States but were then reported in other countries (Berenson 2005b). The transnational nature of dominant pharmaceutical firms thus makes a national analysis of the industry from a realist or neo-realist point of view simply irrelevant.

[40] See Eli Lilly's website: www.lilly.com/about/facilities.html, accessed July 2007.
[41] Calculations based on Eli Lilly's *Annual Report 2005* (p.31) and Fortune *100 Best Companies to Work For 2006*.

While state power is far from irrelevant in the global pharmaceutical arena, the dominant actors that should constitute the basis for our analysis are dominant transnational corporations. The neorealist approach that considers that national firms are an instrument for state power has to be turned upside down: in order to make sense of American foreign trade policy, we have to consider that states are political instruments for dominant firms to serve their private interests and increase their control over the knowledge structure. As contends Wallerstein (2004) through his world-systems analysis, firms from dominant states have the possibility to lobby their government to use state-power on weaker states in ways that will serve the firms' interests. Wallerstein refuses, however, the natural conclusion of this claim: firms, not states, are the main units to understand the global economy. Granted, for the purpose of social analysis, the state cannot be always reduced to an economic instrument in the hands of firms and the prolific literature on the roles of the capitalist state is there to prove it. From the perspective of Big Pharma firms, however, those debates are none of their business and, for them, states are only instruments for their corporate ends. In a nutshell, dominant pharmaceutical firms are *transnational* actors. Big Pharma, constituted by sixteen of those transnational actors, control almost two-thirds of the global market shares in pharmaceuticals (Figure 3.3)

Figure 3.3: Drug Sales as a Share of Total Market, 2007



Sources: Cowen and Co. (Investext), Takeda and Bayer corporate websites

The knowledge structure in pharmaceuticals is thus mostly controlled by 16 transnational actors; 16 organizations enjoying important autonomy from states, and constantly aiming at restructuring the knowledge structure in a way that allows them to extend their control even more to obtain greater earning-capacities.

3.3 Types of Drugs: Ethical vs. OTC; Brand-Name Drugs vs. Generics

The global market for pharmaceuticals is divided between prescription drugs, often referred to as "ethical drugs" or "R_X Drugs"[42] and non-prescription drugs, usually called OTC (over-the-counter). This segmentation can differ from one country to the other. OTC drugs are often identified with the consumer health industry as to distinguish it from the prescription-bound pharmaceutical industry. OTC drugs can be, for example, sunscreens, anti-microbial and anti-fungal products, external and internal analgesics, shampoos containing coal tar, mouthwash, cough medicines or topical products with a therapeutic effect. The frontier is often blurred between OTC drugs and food products or beauty products, since non-pharmacist retailers can sell them. Also, some firms with important sales in OTC products, such as Procter and Gamble or Bayer, do not focus on the NAICS 3254 group (Pharmaceutical and Medicine Manufacturing) but produce mainly in other NAICS 325 groups (Chemical Manufacturing)[43].

The value of global OTC sales depends on what is considered as OTC drugs. For 2004, *The Economist* (2006) values at $117 billion the global market for OTC drugs, whereas IMS, using a narrower definition, values it at $60 billion. OTC drugs thus represent between 11% and 19% of global sales, the rest being ethical drugs. Less important financially than the ethical drug industry, the OTC drug industry is also less glamorous for pharmaceutical researchers, who generally prefer to work on "important" drugs. For example, a running joke

[42] R_X is the derivation of an astrological symbol used for the first prescriptions for talismanic reasons. The symbol R_X was then used to abbreviate the Latin word *Recipe* (take, in its imperative form).

[43] The North American Industrial Classification System (NAICS) was developed by the U.S. government to facilitate the evaluation of national economic performance. I use here the categories contained in the NAICS 2002 Manual and used by the US Census Bureau: www.census.gov/epcd/naics02 . The NAICS is a classification for statistical purposes, but what is called "pharmaceutical firms" do not necessarily confine their production to the NAICS 3254 category; instead, they produce whatever can be profitable using their assets.

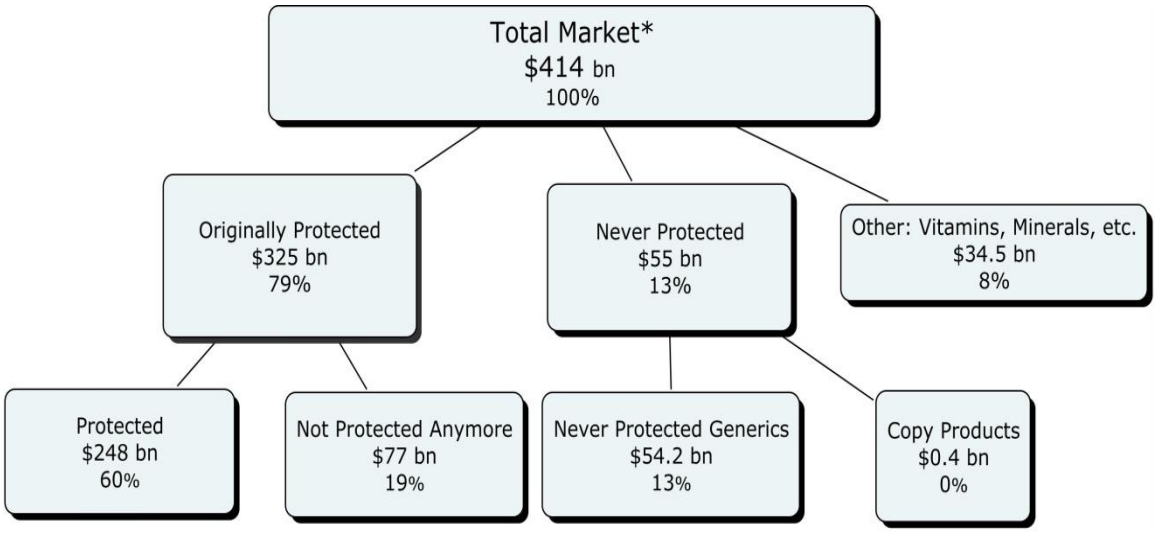
in an OTC U.S. firm: “If the customer takes our syrup, his cold will go away in seven days; if he doesn’t, it’ll go away in a week” (quoted in *The Economist* 2006, 61).

Drugs are normally sold to wholesalers, who then sell to pharmacists or retailers. Some, however, are also sold directly to hospitals. While hospitals may buy important volumes of pharmaceuticals, they usually buy generics at lower prices than pharmacists pay, and thus represent a relatively small share of the market. For example, in Canada, pharmacists and retailers bought 90% of all pharmaceuticals (in value), while hospitals bought only 10% (IMS Health Canada 2006). According to documents obtained by *La Presse* (Noël 2003a) from *Approvisionnements Montréal*, which buys medications for hospitals in Montreal, this organization usually pays 40% less for drug units than the RAMQ (Régie d’Assurance-Maladie du Québec), which already buys medications at the lowest price offered by manufacturers.

Prescription drugs and OTC drugs can be either brand-name drugs or generic drugs, often referred to as “no name drugs”. A generic is a drug that replicates a brand-name product for which IP protection has lapsed. A protected drug is usually protected through patents, but it can also have other forms of protection, such as data exclusivity, marketing exclusivity, pediatric exclusivity, SPC (Supplementary Protection Certificate), etc. Without protection, other manufacturers can produce the same drug and offer it at a lower price than the original since they do not have to duplicate the cost of R&D, or sometimes even the costs of marketing, and they can choose to sell the drugs at lower profit margins. In several major markets, such as Canada, Germany and the U.K., generics account for at least 40% of prescriptions and they now account for 50% of prescriptions in the United States (PICTF 2006, 36). The worldwide generic drugs market, while important in volume, is much less

important in value since, in 2003, it represented $43.4 billion in sales, as compared with $466.3 billion in total sales for pharmaceuticals. Thus generics accounted for only 9.3% of the global pharmaceutical market in 2003[44]. Figure 3.4 shows the market segmentation between protected drugs and generics for the top 8 markets, which are the United States, Canada, France, Germany, Italy, Spain, United Kingdom and Japan.

Figure 3.4: Market Segmentation of the Top 8 Markets in 2005
(United States, Canada, France, Germany, Italy, Spain, United Kingdom and Japan)



* Excludes non-R_X bound

Source: MIDAS New Market Segmentation Feature (cited in IMS 2006)

[44] Calculations based on *Business Communications Company* (cited in Mergent 2003, 13) for sales in generics, and IMS for total sales.

In figure 3.4, "Originally Protected" drugs are brand-name prescription products and include both actually protected drugs and drugs for which protection has lapsed. "Never Protected" drugs are normally prescription generics but may also be "Copy Products", which are drugs launched before protection has lapsed for the original product. "Other" refers normally to OTC drugs sold with a prescription. The bulk of the GPB is thus clearly the brand-name prescription market, which itself comprises more than three-fourths of the global R_X drug market, and around two thirds of the global drug market.

Generics, however, are considered to be the driving force for competition in the pharmaceutical business, constantly forcing companies to research new or improved drugs. When a new drug is discovered, a product patent[45] is usually provided for a period of 20 years, which includes the necessary time for clinical trials before bringing the drug to large-scale manufacturing. According to PhRMA (2006, 8) it takes 10 to 16 years to develop a new drug from the earliest stage of compound discovery to its approval by regulatory agencies, a significant part of the patent term is lost before the new drug can enter the market. However, different laws were implemented in many countries in order to extend the life of patents. For example, in the United States, the effective average patent life for new drug introductions went from 11.4 years in 1993 (Grabowsky and Vernon 1996) to 15.4 years in the late 1990s (NIHCM 2000).[46] After the patent expires, if no new form of protection is obtained, generic competition offers the same medicines at lower prices, forcing brand name manufacturers to

[45] Compound patents differ from process patents. A compound patent is a monopoly right over the distribution of the compound, however it is produced. A process patent is a monopoly right over a way to produce a compound. A process patent provides a monopoly over the production process for the compound and thus allows other firms to compete by creating new and cheaper production processes. The process patent, previously favored by developing countries since it provided an incentive for price competition, is now considered insufficient under TRIPs and has to be supplemented with a compound patent.

[46] Note that the Tuft Center for the Study of Drug Development also reported in 2000 that the average time for clinical development has shortened in the 1990s from seven to five years, and the average FDA approval time has shortened from three years to about one (Kaitin 2000).

create new compounds to maintain high markups. When a drug goes off patent, the first generic competitor usually drops prices by 30% while mature generic competition (with five or six competitors) typically brings down the charge by 70% to 80% to the consumer (Weissman 2002).

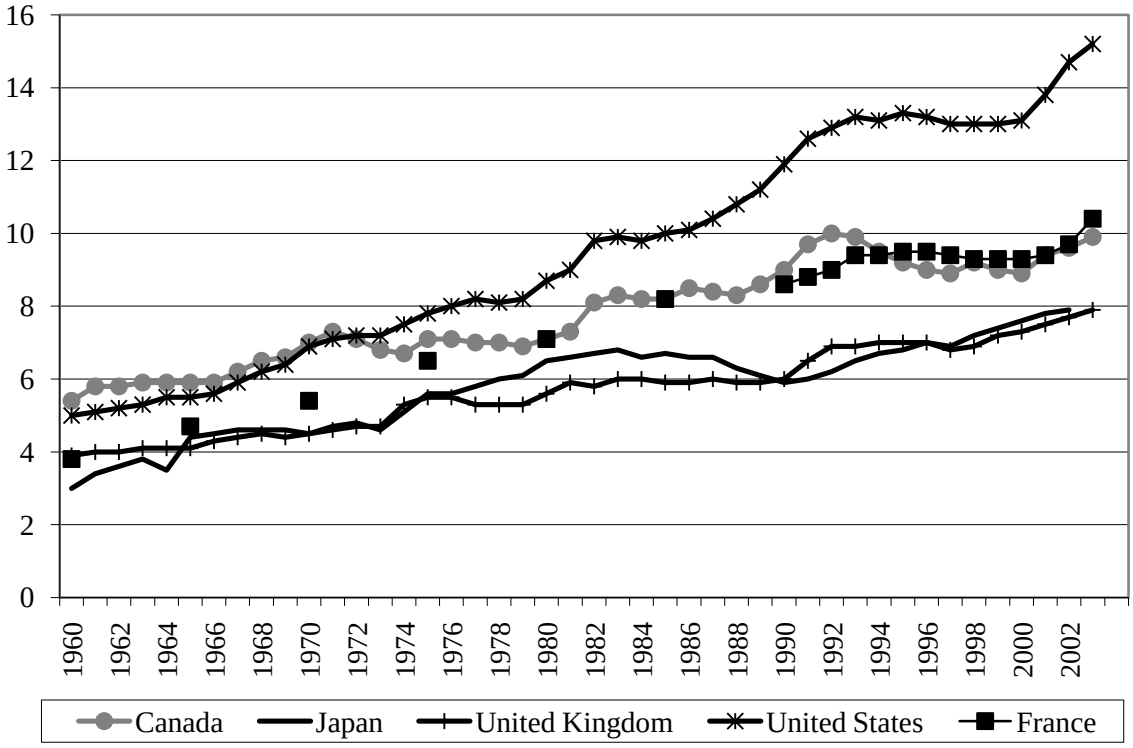
While generic manufacturers are often contrasted with Big Pharma, which includes the most important producers of brand-name drugs, Big Pharma itself also produces a growing proportion of generics on the market (Bloomberg 2005). For example, to prevent competitors from reproducing drugs as soon as they are off patent, there is a growing trend towards the production of authorized generics (or "pseudo-generics"). Under an authorized generic arrangements, brand-name manufacturers license or cross-license the distribution of its brand-name drug to a generic manufacturer or to another brand-name manufacturer in order to maintain some royalties. Alternatively, the brand-name manufacturer simply releases its own generic version of its brand-name drug. This practice creates an important barrier to entry at the expense of generic manufacturers. In Canada, brand-name manufacturers captured in this way approximately 25% of the total generic sales in markets where generics began competing in the last five years (Hollis 2003). In some cases, in the U.S., the brand-name manufacturer simply paid generic manufacturers to stop producing the generic version of their product (Stolberg and Gerth 2000; Boast 2001; Carreyrou and al. 2006). In all cases, the market shares according to market segmentation show that brand-name drugs segment, dominated by Big Pharma, is the crux of pharmaceutical accumulation, while Big Pharma also manage to obtain an important share in other segments.

3.4 Higher Prices for Greater Innovation?

National expenditures on health and, in particular, on pharmaceuticals have been rising constantly in most OECD countries in the late 20th Century. From an industry perspective, rising expenditures in pharmaceuticals simply reflect rising prices due to rising costs in pharmaceutical R&D. If high prices bring high profits, industry lobby organizations, such as PhRMA or R_X&D, claim that high profits are necessary in order to increase investments in R&D and produce new drugs. This common argument is important since the association of today's profits with tomorrow's patients well being is the normative underpinning for the high profitability in the pharmaceutical industry. Without this justification, there would be no reason to extend monopoly rights and it would be publicly much more acceptable to reduce IPR, even if that would mean reducing drug prices and profitability for drug companies.

Today, most industrialized countries are confronted with a steep rise in health expenses, particularly pharmaceutical expenses. Health expenditures now represent a share of GDP two to three times larger than what it was in 1960 (figure 3.5). According to the U.S. Census Bureau, health expenditures in the United States were $1,679 billion in 2003, which is more than the budget for defense and education combined.

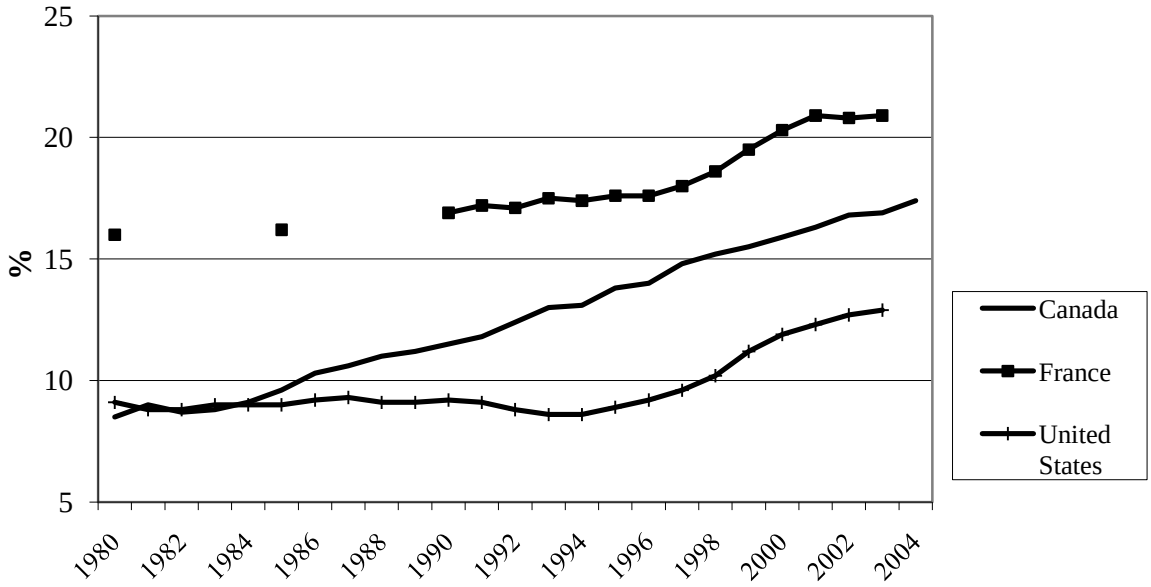
Figure 3.5: National Health Expenditures as Percentage of GDP, 1960-2003
(in selected OECD Countries)



Source: OECD Health Data

A number of different explanations have been proposed for this growth, among them increasing population, aging population and the increasing number of services used by individuals, medicalization of everyday life (Moynihan and Cassels 2005; Pignarre 2001), widening social security coverage, increasing litigation against physicians (Bush 2005), and rising costs for new treatments. Among the different types of health expenditures, pharmaceuticals contribute proportionally more to the rise of expenditures since 1980. In effect, pharmaceuticals constitute a rising share of national health expenditures for industrial countries (Figure 3.6).

Figure 3.6: Pharmaceuticals' Share of Total Health Expenditures
(in Canada, France and United States)



Source: OECD Health Data

In Canada, the annual growth rate for drug expenditures is on average twice the growth rate for health expenditures. Those rising expenditures in pharmaceuticals mean more revenues for the GPB, but the business lobbies justify those rising expenditures for two reasons: 1) "avoided costs"; and 2) rising expenditures in R&D. The advocates for Big Pharma argue that increased expenditures for medicines decrease the general cost of the health system. The rising cost of new medicines thus is justified by the "avoided cost", which would have been the cost of an alternative treatment (Lichtenberg 2000). As Kolassa (2001, 10) explains:

> The prices of new medicines reflect the value they bring to the marketplace, relative to other drugs and interventions. In straightforward terms, if the cost of using a product is lower than the cost of not using it, the price is appropriate and the product delivers real value. Using the economic value of the drugs to assess their prices, one could argue that many, if not most, new drugs are actually underpriced, relative to the value they provide, in terms of reductions in the use of other medical interventions and the improvements in patient health and quality of life.

While this argument seems convincing in terms of standard economic analysis, it is simply biased. As St-Onge remarks (2004, 33), this economic logic would also mean that we should increase the price for healthy food because it reduces health costs. What would happen if the price of air was determined by the cost of its alternatives? According to this logic, we could charge just about any price for a life-saving drug like insulin, because death would the only alternative treatment.

The second argument used to justify the steeply increasing cost of medicines is more important: to pay the rising costs of R&D, companies must have higher profits; and to have higher profits, companies must demand higher drug prices[47]. Rising costs of production, it is claimed, justify rising expenditures. To test this argument it is necessary to measure the R&D cost of each new drug. Before exploring this point, however, it is important to understand how contemporary medicines are developed, and what costs are associated to that production.

[47] Note that higher profits are not justified here as the productive outcome of investments in R&D. They are justified, instead, through the Keynesian propensity to consume, under which theory rich people invest and poor people consume. Higher profits for investors provide more money to richer people, who will invest more to produce medicines. Realized profits, and not expected profits, become here the necessary conditions for investment. This logic is part of the neoliberal discourse where technological innovation is considered to be the consequence of higher profits rather than the cause (see Gagnon 2008a).

Developing Medicines: The Pipeline

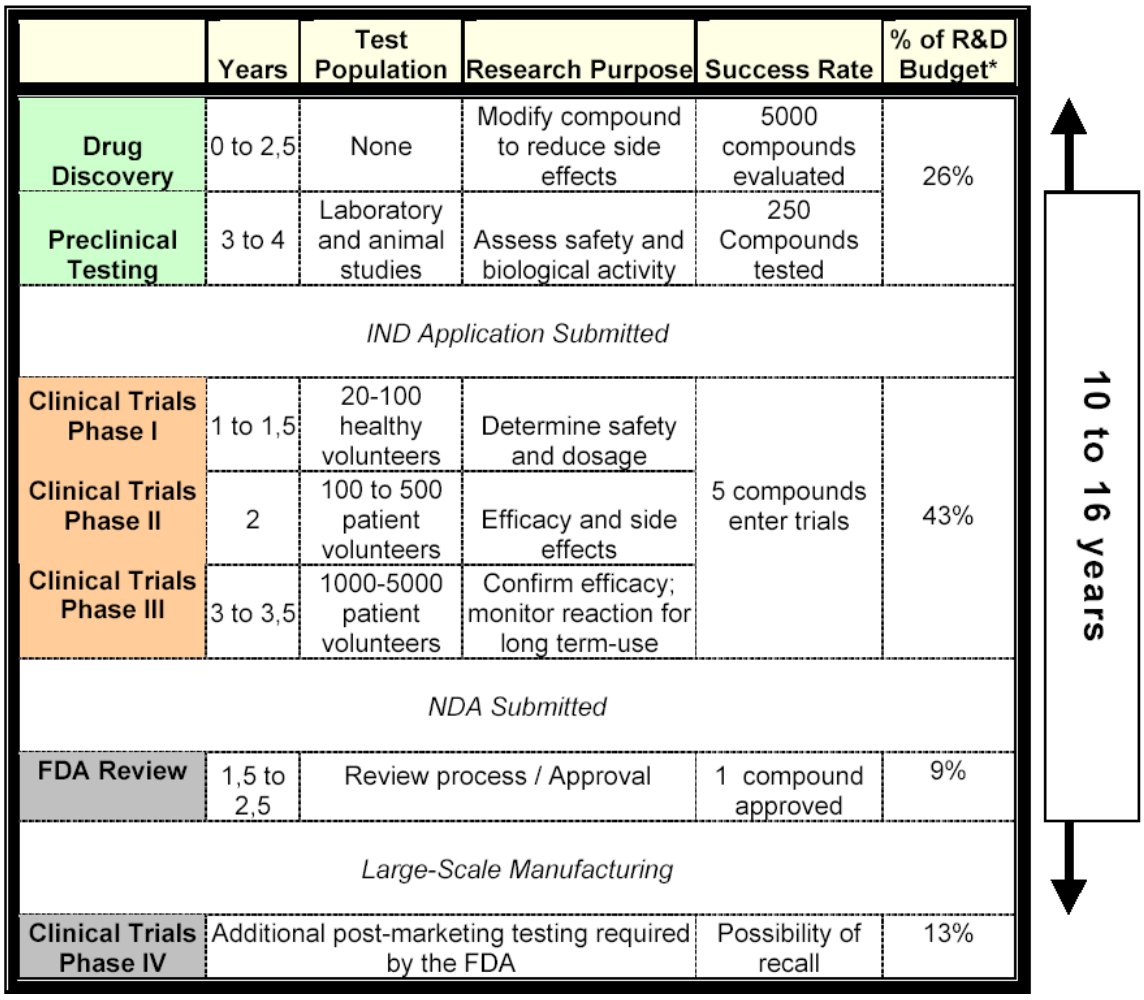
The regulatory process for approving new compounds, which the pharmaceutical industry calls the "pipeline", largely determines the cost of creating a new drug. The pipeline is the process by which a new drug is developed then approved through clinical trials. This process came to dominate drug development in the 1970s for security reasons after an approved drug in the 1960s, thalidomide, was found to cause fetal deformities, and also because of the general rethinking of the methods by which to assess new medicines due to new technologies. The method of blind trial and error through which most drugs were discovered before the 1960s was thus replaced by a more rational and safer mode of assessment. Under the new mode, modern randomized clinical trials (RCTs) became mandatory in order to provide an accurate statistical measure of a drug's safety and therapeutic value under controlled conditions as compared to a placebo[48]. The implementation of this new assessment method would transform the process of discovery itself.

Those RCTs are the core of the pipeline that runs from the discovery of a new drug to post-marketing testing. In the United States (Figure 3.7), the pipeline process can take 10 to 16 years, whereas a patent filed after discovery of a given compound protects the substance for twenty years. The situation is similar in Europe, where the length of time necessary to bring a product to market after the synthesis of the new active substance is on the average 12-13 years (EFPIA 2005, 18).

[48] The RCTs done before a drug comes onto the market involve usually between 4000 and 6000 patients. It can only identify relatively common side effects (i.e., those occurring in about 1:1500 to 1:2000 patients) and assess the efficacy of the drug. There is an important distinction that is made, however, between efficacy and effectiveness. Efficacy is how well the drug works in the world of clinical trials where conditions are tightly monitored and patients are carefully selected. Effectiveness is how well the drug works in the messy real world. Effectiveness is assessed partly through post-marketing clinical trials, also called Phase IV clinical trials.

Figure 3.7: The American Pipeline

US Drug Approval Process in 2005



	Years	Test Population	Research Purpose	Success Rate	% of R&D Budget*
Drug Discovery	0 to 2,5	None	Modify compound to reduce side effects	5000 compounds evaluated	26%
Preclinical Testing	3 to 4	Laboratory and animal studies	Assess safety and biological activity	250 Compounds tested	
IND Application Submitted					
Clinical Trials Phase I	1 to 1,5	20-100 healthy volunteers	Determine safety and dosage	5 compounds enter trials	43%
Clinical Trials Phase II	2	100 to 500 patient volunteers	Efficacy and side effects		
Clinical Trials Phase III	3 to 3,5	1000-5000 patient volunteers	Confirm efficacy; monitor reaction for long term-use		
NDA Submitted					
FDA Review	1,5 to 2,5	Review process / Approval		1 compound approved	9%
Large-Scale Manufacturing					
Clinical Trials Phase IV	Additional post-marketing testing required by the FDA			Possibility of recall	13%

10 to 16 years

*: 9% uncategorized

Sources: PhRMA, FDA

The pipeline can be divided into two important periods (Lavigne 2006, 18-22): 1) the discovery period (preclinical R&D), and 2) the clinical period (clinical R&D). In this discovery period, researchers mainly endeavor to identify a biological target (what causes the illness) and relate it to a molecule or compound, called a *lead compound* that produces an

effect on the target. During the discovery period, researchers try to modify and adapt the lead compound to obtain desired effects and to discard undesired effects.

The second period is the most important in terms of R&D. Through phased clinical trials, researchers determine if the new treatment (the lead compound) is safe and efficacious in a controlled environment. In Phase I clinical trials, they determine first the safety of the drug on human beings. In Phase II clinical trials, they examine the drug's therapeutic effect versus secondary effects. Then, when the drug is considered safe and efficient in the short-run, they bring it to Phase III clinical trials, which are large-scale trials to more accurately determine the drug's efficacy and main secondary effects. Note that a new drug with little incremental utility, compared to a placebo, usually necessitates larger Phase III clinical trials in order to provide the statistical significance to validate the claim that the drug should be marketed[49]. When Phase III is over, the company can apply at the FDA for a NDA (New Drug Application), and the results are analyzed by regulatory authorities, which then either approve it for marketing or reject it. After marketing begins, post-marketing clinical trials (Phase IV clinical trials) are requested to obtain more information about risks, benefits and optimal use. Note that a Phase IV clinical trial may often become a disguised means of promoting the drug; it is then considered a "seeding trial" in which the pharmaceutical firm invites doctors to prescribe the drug for clinical trials, but with the unstated purpose of inculcating a habit of prescribing the drug (Angell 2004, 161-172).

[49] A drug is generally not assessed by comparison to existing medicines but only by comparison with a placebo. When the drug is being compared to another drug, most trials are designed as non-inferiority trials, i.e., to show that the two drugs are more or less equivalent. Non-inferiority trials are much smaller than superiority trials and therefore much less expensive to run. However, drug firms may sometimes run superiority trials to provide better arguments for marketing purposes.

This process of developing a new drug is certainly long and costly. Each company has its own pipeline; its network of researchers and doctors used to develop and test its new drugs. The pipeline, however, is very demanding and the reigning ideology among investors is that it becomes profitable only when there are always compounds under assessment at every phase of the pipeline. An empty phase means unemployed capacities and expensive delays before bringing new drugs to the market. The pipeline, in order to assure investors that the firm aims at maximizing their profits, requires the discovery of new drugs at a very fast rate, and since important new drugs usually take longer to be discovered, the pipeline favors the development of "successors" to existing drugs, instead of radically new medicines. The production process is thus organized along the lines of a business model that fits the short-term interests of investors, as compared to long term interests of patients. As Pignarre argues (2003), clinical trials do not only select drug compounds, they also select research methods to favor those who can provide the necessary amount of drug compounds for the pipeline. Since investors demand pipelines that are constantly full, research programs for radically new drugs, which produce fewer compounds than those based on existing drugs, are more likely to be abandoned (Pignarre 2003, 67, author's translation):

> [The method of clinical trials] determine which research programs receive funding, even for research far upstream of clinical trials. It favors technologies that produce a good output of testable compounds. Research laboratories in the pharmaceutical industry resemble more and more to an assembly line where a maximum of operations are automated and repetitive. It is certainly the best way to find new compounds, but the only flaw is that it is difficult to distinguish those new compounds from existing drugs.

Financial consultants for the GPB understand that the pipeline, with its clinical trials, does not just test in order to develop new drugs; instead, the pipeline forms the industrial core of the business where the industry (researchers, doctors, engineers) may be molded to favor the firm's financial interests. It is the core of the knowledge structure in pharmaceuticals. Everything is organized to produce a greater amount of NDAs, even if the incremental therapeutic value of a new drug is negligible. Clinical trials, as a method for assessing new drugs, thus have transformed the whole process of R&D and discovery. The result is that the bulk of pharmaceutical innovation nowadays provides little significant therapeutic improvement. In the words of Bill Burns, chief of Roche's pharmaceutical division, the dominant business model in the production of new drugs is "the 'me-slightly-different-marketed-like-hell' model" (quoted in Alpert 2005).

The Cost of Producing New Drugs

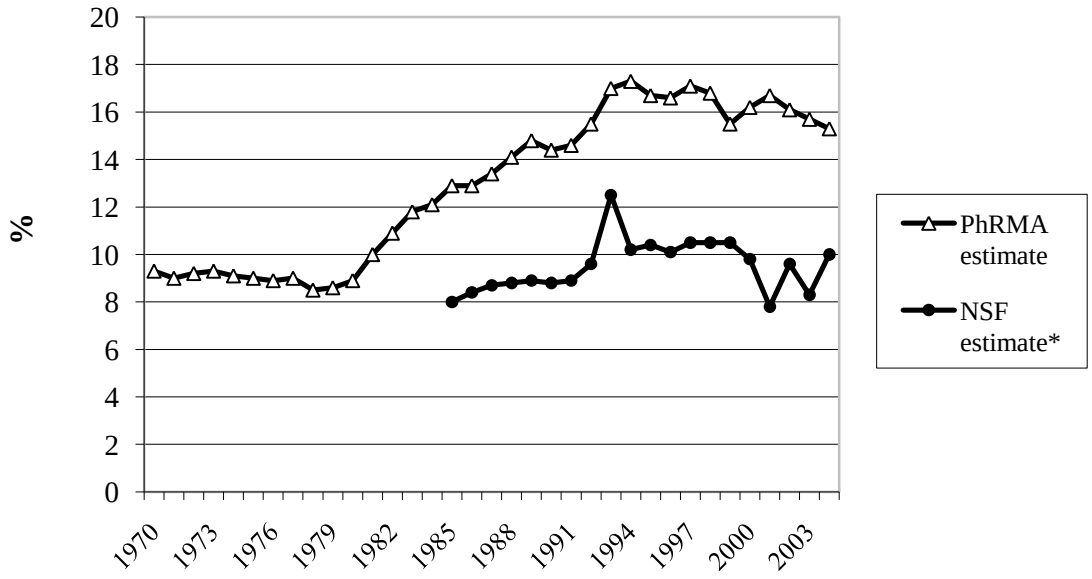
The main argument to justify the high prices of pharmaceuticals (and the high mark-ups) emphasizes the high cost of R&D in the production of new drugs. It is generally accepted that the nominal production cost of each new drug has risen steeply since 1980. However, accepting this claim at face value is problematic, since there are no solid data to support it. PhRMA reveals (PhRMA 2006) that its members' total investment in R&D went from $2 billion in 1980 to $37 billion in 2004. However, since the membership of PhRMA also evolved and expanded since 1980, it is difficult to know if the increased number is due to increased R&D spending or to increased membership. The ratio between R&D expenditures and sales is more relevant. This ratio increased in the 1980s, but also constantly decreased since 1994. This increase of the R&D/Sales ratio in the 1980s can be explained partly with

the emergence of new technological opportunities with biotechnologies but also with the implementation of important tax credits for R&D in the 1980s and the extension of patent life through the 1984 Patent Restoration Act. For example the *Economic Recovery Tax Act* of 1981 and the *Orphan Drug Act* of 1984 made R&D expenditures deductible from capital's income; R&D firms received a 20-25% tax credit and had access to a 50% tax credit in the case of orphan drugs. Ultimately, one must also question the accuracy of the PhRMA data, since the lobby has a great interest in overestimating spending on R&D. Not surprisingly, the National Science Foundation (NSF), which is an independent U.S. government agency responsible for promoting science and engineering, provides much smaller estimates of R&D as a percentage of sales since 1985 (figure 3.8). Significantly, however, the NSF data also show a decline since 1993.

In figure 3.8, The PhRMA estimate is based on the declarations by firms themselves. The OTA explains (1993, 40) that estimates of total R&D expenditures built from individual firms financial records are usually overstatements because of certain accounting practices that leads to double counting such cost at the industry level. Specifically, purchasing the right to further develop a product is considered, according to accounting practices, to be the purchase of "in-process R&D". For example, if a company synthesizes a new compound and licenses it to another company for clinical trials and marketing, the former declares its R&D expenditures while the latter also declares the amount paid as "in-process R&D", thus counting twice the same expenditure in R&D. In the same way, when one pharmaceutical firm acquires another one, it involves a double counting of R&D, since the purchaser declares an amount in terms of "acquired in-process R&D". Since both mergers and acquisitions and cooperation agreements accelerated since 1980 (see chapters 5 and 6), it

directly increased the ratio of R&D on sales for pharmaceuticals, which explains partly the important increase in this ratio within PhRMA data. The NSF estimate, which avoids such double counting, has to be considered much more accurate. The NSF also provides data that compare pharmaceuticals with other R&D oriented sectors (Figure 3.9).

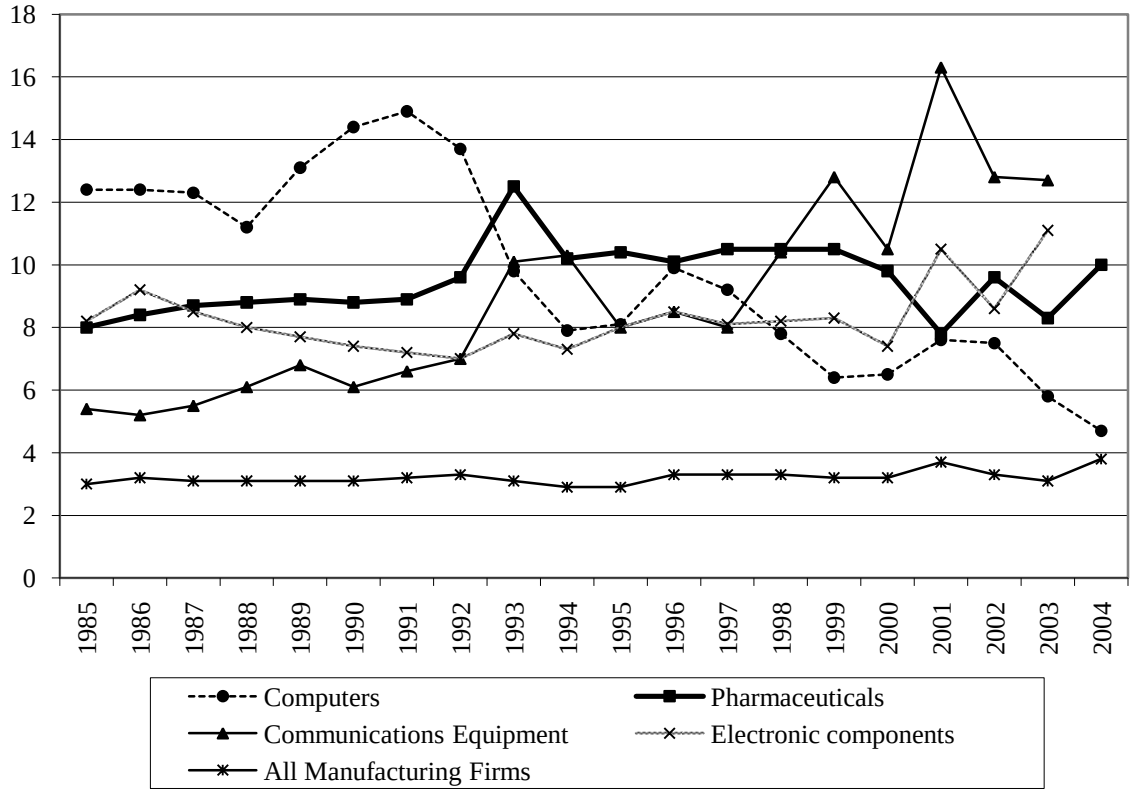
Figure 3.8: Research and Development Spending as a Percentage of Sales in the American Pharmaceutical Business (1970-2004)



*: The NSF data are in two series: 1985-1997 based on the SIC and 1999-2004 based on the NAIC. Since no data were available for 1998, I used the average of the 1997 and 1999 values.

Sources: PhRMA 2006, NSF 2000; 2006a; 2006b.

Figure 3.9: Research and Development Spending as a Percentage of Sales in Different American Business Sectors
(1985-2004*)



*: The NSF data are in two series: 1985-1997 based on the SIC and 1999-2003 based on the NAIC. Since no data were available for 1998, I used the average of the 1997 and 1999 values. No estimate was reported in 1991 for communications equipment, I used the average of the 1990 and 1992 values for that industry.

Sources: NSF 2000; 2006a; 2006b

The figure 3.9 demonstrates that PhRMA's contention that its members have experienced an extraordinary increase in R&D as a percentage of sales since the 1980s is comparatively overstated. Between 1985 and 2004, the pharmaceutical sector increased its R&D spending as a percentage of sales by 25%, which is less than other sectors like communication equipment (135%), electronic components (35%) and all manufacturing firms (27%).

While increased R&D spending does not conclusively explain why prices and profits increase faster for pharmaceuticals than other sectors, the industry also favors an explanation based on the measurement of production costs for new drugs. There are two ways to measure this (OTA 1993): 1) By looking at aggregate numbers on an industry-wide basis, or 2) by sampling drug costs at the level of individual firms. The first method, used by Baily (1972), Schwartzman (1975), Wiggins (1987), Grabowski and Vernon (1990) and Matthews (2002), is to relate the total amount of R&D spending to the number of drugs approved by the FDA, either through linear regression or by dividing the two on an annual basis. The results obtained for the United States show quickly rising costs (Table 3.4).

Table 3.4: Average Production Costs for Each New Drug At Industry Level
(United States; 1958-2000)

Author	Years	Average Estimated Cost (Million $)
Baily (1972)	1949-1962	2.5
Baily (1972)	1962-1969	6
Schwartzman (1975)	1966-1972	24
Grabowski and Vernon (1990)	1970-1979	125
Wiggins (1987)	1970-1985	108*
Matthews (2002)	1987-1993	364
Matthews (2002)	1994-2000	611

* Wiggins originally reported $125 Million; adjustment for technical error changes the number to $108 Million (DiMasi et al. 1991).

Sources: OTA (1993) and Matthews (2002)

This method is problematic for, at least, two reasons: 1) all authors need to rely on data provided by PhRMA for total spending on R&D, and 2) annual R&D divided by the annual number of new drugs does not take into account the fact that investments in pharmaceutical R&D are distributed over a long period of time, since it can take up to 16 years of R&D before a new drug emerges from a firms' pipeline. Given these methodological problems, the results obtained to date cannot be considered reliable.

A second method is to take a sample of different drugs and calculate the cost of producing that sample. This method is usually considered more relevant, but few studies have attempted to calculate production costs this way, since pharmaceutical firms refuse to disclose precise spending figures on particular drugs, citing proprietary reasons. Analysts thus need to resort to surveys of firms, without the ability to verify data provided. This method was used by Schnee (1972), Hansen (1979), DiMasi et al. (1991; 2003) and Gilbert et al. (2003), and it renders similar results with steeply rising costs (Table 3.5).

Table 3.5: Average Production Costs for Each New Drug at the Level of Individual Firms in the U.S. (1950-2002)

Authors	Years	Average Cost (Current Million $)	Average Cost (Constant 2003 Million $)
Schnee (1972)	1950-1967	0.5	3.4
Hansen (1979)	1963-1975	54	105
DiMasi et al. (1991)	1970-1982	231	343
DiMasi et al. (2003)	1983-1994	802	864
Gilbert et al. (2003)	1995-2000	1100	1180
Gilbert et al. (2003)	2000-2002	1700	1700

Sources: Calculations adapted from OTA (1993) and Dickson and Gagnon (2004).

While the case for a steep rise in R&D costs appears compelling, caution remains necessary. For example, although the Office of Technology Assessment (OTA), which is a department of the U.S. Congress, approved the methodology used by DiMasi et al.[50] (OTA 1993, 15), it nonetheless had serious reservations about the validity of the data. It called into question whether firms themselves had access to accurate data, and whether firms are motivated to provide accurate data (OTA 1993, 60): "[t]he estimates of R&D cash outlays and capitalized costs in the project-level studies are imprecise and potentially biased, but the magnitude and net direction of these errors cannot be predicted". The studies by Hansen (1979) and DiMasi et al. (1991; 2003) became authority in the industry, and it is now assumed that the cost to produce a new drug is now more than $802 million (Goozner 2004). The study by Gilbert et al. (2003), from the Bain Consulting Group, builds on the DiMasi data, but additionally takes into account launch costs and the rising failure rate in recent years. According to these data, the cost to develop a new drug increased by 1600% between 1975 and 2002. Authors who accept these data thus suggest that there is a "crisis" of productivity in the pharmaceutical industry, as R&D costs rise with fewer innovative drugs in the pipeline (Matthews 2002; DiMasi et al. 2003; Gilbert et al. 2003; Lavigne 2006). The claim of a "productivity crisis" is often used to justify the rising prices of pharmaceuticals in order to pay for the increasing costs of production of new drugs. However, one should keep in mind that this "crisis in productivity" is not related to a business crisis in terms of profits, as shown with the increasing differential earning-capacity for Big Pharma. This crisis in

[50] DiMasi et al. analyzed R&D expenditures for 93 self-originated NCEs (not all successful) from 12 firms, using a 9% rate for the opportunity cost of capital.

productivity is thus less related to a lack of profit, than to a dominant business model that provides no incentive for greater innovation.

Many analysts have sharply criticized the studies by Hansen and DiMasi. First, those studies were produced by the *Tufts Center for the Study of Drug Development*, which, while associated with Tufts University, obtains the bulk of its resources from pharmaceutical firms. While this does not *necessarily* translate into bias, data provided from undisclosed private sources raise obvious concerns around conflict of interest. There are a range of additional considerations to bear in mind when reviewing the Tufts Center studies:

> 1) The studies do not consider tax deductions for R&D. According to the OTA, a pre-tax R&D cost of $359 million would become an after-tax cost of $237 million, a decrease of 34% (OTA 1993, 69).
>
> 2) The bulk of R&D costs constitute the opportunity costs of capital[51], which account for 51% of DiMasi's total figure (Public Citizen 2001a, 2). The opportunity cost used is 11%; a variation of 0.5% would represent a difference of $25 million (Prescrire 2003, 785).
>
> 3) The total cost of new drugs includes the costs of failures since the total is based on all outlays before a single compound is marketed.
>
> 4) The estimated costs are for New Chemical Entities (NCE), which are drug compounds that have never been marketed before. NCEs represent only 35% of all new drugs approved in the United States between 1990 and 2004 (Lexchin 2006, 573).
>
> 5) Only drugs that were fully developed in-house were included in the study, whereas most drugs are at least partially financed by public funds (Prescrire 2003, 784), especially for basic research. Public money accounts for 84.2% of world basic research budget for health (Light 2006, 35). The costs of NCEs developed in-house are 3.7 times higher than the costs of typical new drugs (Light and Warburton 2005a, 1031).

[51] The opportunity cost of capital is the income one would have received if he/she invested somewhere else. It is not an outlay.

> 6) The costs of R&D include Phase IV clinical trials that are often used for "seeding trials", which are clinical trials for promotional purposes (Light and Warburton 2005b, 1047).
>
> 7) The FDA allows priority review for NCEs that represent major therapeutic advances, for example for rare diseases. Priority review is a fast-track to allow marketing; it demands smaller clinical trials and thus smaller R&D expenditures (Palmedo 2006; Love 2006).

Most companies with NCEs that are less important in therapeutic terms often choose to run not only the standard clinical trials, but also the bigger Phase III and Phase IV clinical trials for marketing purposes. With bigger clinical trials, firms can provide better marketing claims for prescriptions even when a drug's incremental therapeutic value is almost insignificant. On this question, *The Wall Street Journal* has recently cited Pharma executives on the issue of Phase III clinical trials (Langreth 1998):

> "The FDA told us that we don't need all these trials" to get omapatrilat approved for blood pressure, says Hubert Pouleur, Bristol-Myers' vice president for cardiovascular clinical research. "But there is a difference between getting a drug approved and having it be a commercial success. A new drug will be used only if it is a significant improvement on existing drugs, and to establish that you need trials that aren't required for approval."

Additionally, other Pharma executives were cited in relation to Phase IV clinical trials (Langreth 1998):

> Postmarketing studies, as trials for drugs already on the market are called, "are billowing out of control," says Eve Slater, Merck's senior vice president for clinical testing. She decries "a total lack of science" in some studies. But drug marketers contend they are helpless to stop the one-upmanship. If a rival mounts a new study aimed at backing up a sales-expanding marketing claim, "you have to do it, too, or you are dead in the water," she says.

The situation seems paradoxical: new drugs with important incremental therapeutic value are cheaper to produce in terms of drug unit, but since research programs for radically new drugs usually produce fewer compounds for the pipeline, they are less profitable. Given investors' imperative for a full pipeline, research programs for more innovative drugs are thus replaced by more profitable ones producing me-too drugs. Bearing in mind these considerations, the only conclusion possible is that there are no solid conclusions about R&D costs on new drug compounds. Data cannot be verified, and after one accounts for inflation, tax credits and incentives, opportunity costs and public spending, it is possible that the remaining increase in the production costs is primarily related to the fact that new drugs generally have less important therapeutic value. As such, while increased spending on pharmaceuticals constitutes an important part of rising health expenditures, it cannot be argued that rising drug production costs on new medicines form the main reason for growing pharmaceutical prices, as PhRMA and R_X&D contend. Instead, the analysis here suggests that a growing part of the costs in R&D focuses less on innovation than on marketing purposes, and that the financial imperatives of the pipeline causes a qualitative decrease in innovation.

3.5 Assessing Pharmaceutical Innovation

The suggestion that the quality of pharmaceutical innovation has declined in relation to the demands of the pharmaceutical pipeline system has been evidenced in some recent studies. As such, many analysts (Reis-Arndt 1987; Redwood 1987) endeavored to evaluate

the importance of new drugs developed since the 1960s, usually basing their assessment upon commercial value instead of therapeutic value. As previously explained, however, linking a drug's therapeutic value to its commercial success can be misleading. Money does not measure innovation, and this section aims to measure therapeutic innovation in industrial (or technical) terms, both qualitatively and quantitatively, without reference to commercial value.

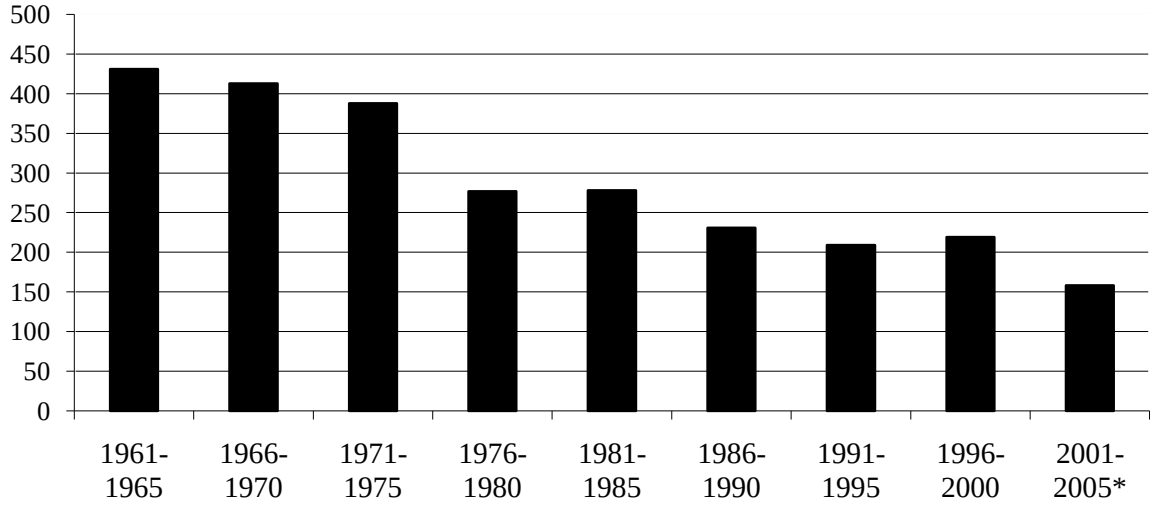
Quantitative Evaluation of Pharmaceutical Innovation

Even with research methods focusing on imitative drugs in order to keep the pipeline well-supplied, there is an important quantitative decrease in terms of new compounds. While historical data for the national introduction of New Chemical Entities (NCEs) exist for most countries, such national data reveal less an evolution of innovative capacity than a transformation in the regulatory authorities that approve new drugs. As such, the most significant quantitative data for pharmaceutical innovation is the number of global market introduction of NCEs since such data remove any distortion due to national regulatory authorities. The global introduction of NCEs in the pharmaceutical industry serves as an index to measure innovation with no reference to money value; it provides an approximate measurement of the quantitative industrial output of social wealth in pharmaceuticals.

The data for global introductions of NCEs are not easy to isolate. From 1961 to 1985, the only comprehensive global analysis available is in German (Reis-Arndt 1987), although the data are quoted and translated in Redwood (1987). From 1982 to present, the data are available through the New Product Focus database, provided by IMS, but cannot be used for academic purposes due to prohibitive cost. Fortunately, IMS agreed to provide the author the

latest data from 2000 to 2005 (IMS Health Canada 2006), and a recent scientific article for the first time reproduced all data from 1982 to 2003 (Grabowski and Wang 2006). Using all these sources, the overall portrait of the evolution of pharmaceutical innovation in quantitative terms is attainable (figure 3.10).

Figure 3.10: Global Introductions of New Chemical Entities, 1961-2005



*: The data used for 2004-2005 cover all New Molecular Entities (NME) instead of NCE. NMEs include NCEs and also new drugs obtained through biotechnology, called New Biological Entities (NBE).

Sources: 1961-1985: Erika Reis-Arndt (1987) quoted in Redwood (1987);
1986-2003: IMS Lifecycle New Product Focus Database in Grabowski and Wang (2006); 2004-2005: IMS Lifecycle New Product Focus Database in IMS Health Canada (2006).

The pharmaceutical industry now produces almost three times fewer new compounds than it did in the sixties. Nonetheless, by itself, this analysis only in quantitative terms is inconclusive, since fewer compounds of great importance could provide more benefits than

lots of futile compounds. This analysis must be supplemented with a qualitative evaluation of the new products.

Qualitative Evaluation of Pharmaceutical Innovation

Clinical trials could allow one to evaluate statistically the therapeutic value of new drugs in comparison with existing drugs of the same therapeutic class. Most clinical trials, however, compare new compounds only to placebos and do not allow an evaluation of the improvement of the pharmacopoeia. The best way to evaluate the extent of innovation in pharmaceuticals would be, in qualitative terms, to evaluate independently the importance of each new drug. According to the independent quasi-judicial organization Patented Medicine Price Review Board (PMPRB 2001; 2006), in Canada, only 13 of 181 (7%) new active substances (NAS) showed a "substantial improvement" over placebos and existing drugs in the same therapeutic class, as tested in premarketing clinical trials between 1998 and 2005. PMPRB classified the remaining NAS in the category "moderate, little or no improvement". These numbers are similar to those obtained by *Prescrire*, an independent French medical journal. Each year, the journal comments each new drug available for prescription in France. Since 1981, the journal began to classify each new drug in terms of its therapeutic advance as compared to the existing pharmacopoeia (Table 3.6).

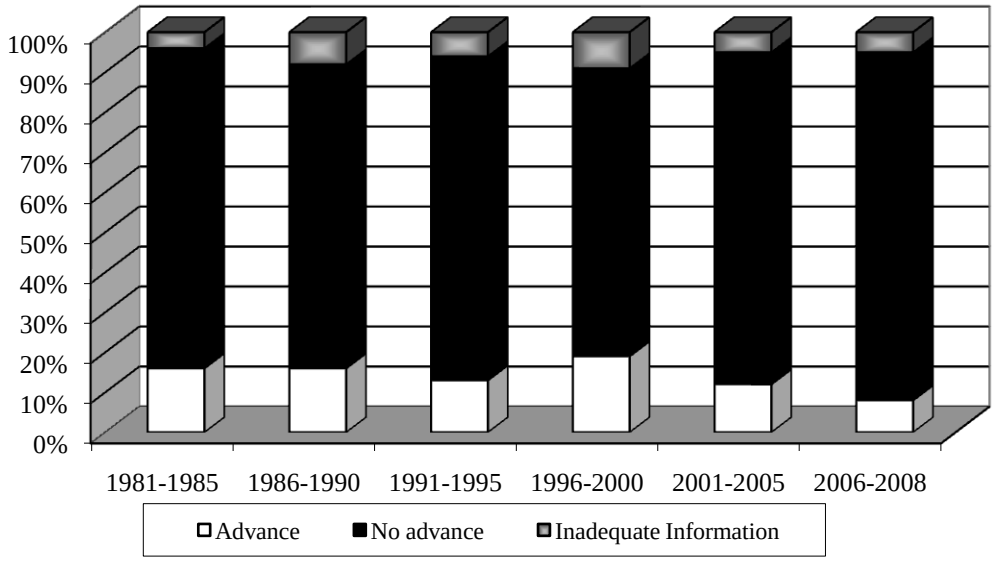
Table 3.6: Classification of New Drugs Available for Prescription in France According to their Therapeutic Advance (Excluding Generics)

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
Major advance	1	5	0	1	0	2
Important advance	16	12	13	26	11	3
Some advance	32	38	59	63	35	28
Eventually useful	62	84	121	130	90	83
No advance	177	165	298	189	184	205
Possible dangers	6	20	20	12	48	65
Inadequate information	12	27	30	40	19	20
Number of new drugs	306	351	541	461	387	396

Sources: Prescrire (#213 p.59; #224 p.56; #280 p.142; #304 p.139).

The table demonstrably shows that the quantity of new drugs is unrelated to the improvement of the pharmacopoeia. For example, 120 new drugs were introduced in 2008 but only 6 showed some therapeutic advance while 23 were considered as more dangerous than helpful by *Prescrire* (2009); concomitant to this, 82 drugs (excluding generics) brought no therapeutic advance. In fact, the *Prescrire* classification shows that as the quantity of new commercially launched drugs increased, their quality plainly decreased. Over the long term, the relative number of significant new drugs in terms of therapeutic value, already low in the beginning of the 1980s, has been declining since 2001 (Figure 3.11).

Figure 3.11: Percentage of New Drugs Representing a Therapeutic Advance in the French Pharmacopoeia, 1981-2008



Sources: Prescrire (#213 p.59; #224 p.56, #280 p.142; #304 p.139).

In the United States, in order to compare the "incremental utility" of recent drugs over older drugs, the FDA implemented in 1976 a system that classifies commercially-sponsored investigational new drug (IND) applications and pending NDAs[52]. The system was replaced, however, in 1992 by categorizing drugs as either "standard" or "priority", which makes long-term comparisons less conclusive. It was assessed, however, that between 1989 and 2000, 77% of all the new drugs approved by the FDA were classified as offering little or no therapeutic gain (Morgan et al. 2006, 22). Such assessment of "incremental utility" began after important criticisms about the therapeutic value of the new drugs appearing on the market.

[52] For a presentation of this classification system and for the results obtained in the 1980s, see Kaitin et al. (1991).

Summed up, pharmaceutical innovation decreased steeply in recent decades, both in qualitative and quantitative terms. Most analysts consider that therapeutic improvement is now much less important than during the 1940s, 1950s and 1960s. During that period, the "therapeutic revolution" (Temin 1980) arising from the discovery of antibiotics led to a "cascade of discovery" (Redwood 1987) in the most significant categories of the pharmacopoeia: Antibiotics, psychotropics, antihypertensives, tranquilizers, antiarthritis, anti-polio vaccine beta-blockers, diuretics, antidiabetics, oral contraceptives (see Pignarre 2003; LeFanu 1999). Some analysts, such as Richard Epstein (2006), blame diminishing innovation on stringent regulatory requirements and clinical trials, imposed since the thalidomide scandal. Such claim, however, provides only a surface understanding of the trend. After all, these regulatory requirements were put in place with the keen support of dominant pharmaceutical firms since such regulations provided Big Pharma an important new barrier to entry, given that increased costs to produce new drugs can kill emerging competitors. Skeptical as one may be about the "crisis of productivity", analyzed in terms of costs of production, it is undeniable that there is a "crisis of innovation" in therapeutic terms, qualitatively and quantitatively. One can only conclude that the whole discourse about the "New Economy", in which profits are now explained by a permanent regime of innovation due to intellectual capital, creativity and other intangible assets, cannot apply to the GPB. The innovation crisis coupled with rising profitability for the GPB makes the "New Economy" discourse fallacious and the rising profitability of the GPB still needs to be explained. The next chapters provide an alternative explanation for this phenomenon of rising profitability coupled with decreasing innovation by understanding in depth the power dimensions involved in the existing pharmaceutical knowledge structure.

4. BIG PHARMA; A BUSINESS ODYSSEY

"People of the same trade seldom meet together, even for merriment and diversion, but the conversation ends in a conspiracy against the public, or some contrivance to raise prices"
-Adam Smith (1776)

"Our Competitors are our friends, our customers are the enemy"
-James Randall (ADM's President, caught on tape in 1995 by the FBI during a meeting of the Lysine Cartel)

Since the late nineteenth century, the pharmaceutical business has been the most profitable manufacturing sector, and the companies included in Big Pharma have been among the leaders in capitalization, multinationalization and export earnings (Liebenau 1987, vii). The Global Pharmaceutical Business (GPB) is today considered to be one of the most dynamic sectors of the KBE due to a relentlessly increasing profitability since the 1980s. As shown in Chapter 3, this rising profitability cannot be explained by a surge in productivity, since the production of new compounds has decreased quantitatively and qualitatively. In fact, it is now common place to consider that the industry is facing a "drug drought" (Pignarre 2003; Le Fanu 1999; Economist 2004; Berenson 2006). Profitability rests here on a different logic than industrial productivity. In order to understand how and why this discrepancy between rising profits and declining productivity is possible, it is necessary to understand how today's power structures in this sector came to be. The recourse to history to account for the power structures in the GPB is essential in order to follow Veblen's inductive approach to economic reality so as to understand the GPB as it is, instead of trying to confine our analysis to a teleological taxonomy (be it neoclassical hypotheses or neo-Weberian ideal-

types). Such taxonomy could taint the analysis, since it often squeezes realities into wishful theorizing and ideologically loaded categories (Veblen 1899-1900; Wesson 1998). The analysis needs to focus on dominant capitalist groups in the pharmaceutical sector, struggling and cooperating in a structural competition to shape the power structures to their own interest. To do so, the analysis must focus specifically on dominant global pharmaceutical firms, which can now be called *Big Pharma*.

Big Pharma went through important structural transformations in the last century, and its history is the history of dominant pharmaceutical corporations that organized and controlled the knowledge structure in pharmaceuticals. Their control and power has never been absolute, however, since different events, internal or external to this sector, have sometimes changed the state of affairs. It is possible to identify three variables, more or less independent, that modified the power of Big Pharma over the pharmaceutical knowledge structure:

> 1) Technological evolution: The evolution of pharmaceutical technology is mostly path-dependent from corporate interests since the rise of corporate research laboratories (the R&D division of corporations) at the beginning of the twentieth century (Noble 1977). However, technological breakthroughs outside Big Pharma can still happen[53]. A major pharmaceutical breakthrough could provide an opportunity for newcomers or supporting firms to overcome barriers to entry and enter the realm of Big Pharma (as Pfizer did with antibiotics, and Amgen with biotech).
>
> 2- Regulatory evolution: Pharmaceutical business is one of the most regulated business and changes in industrial regulations (e.g. regulations for drug safety) or in business regulations (e.g. tightening or loosening of IPR regulations) has transformed the level of power of dominant corporations over the

[53] The idea that there is always a possibility that technological innovation does not necessarily reflects commercial interests was developed by Thorstein Veblen. For Veblen, the "instinct for idle curiosity" is the non-profit driven human crave for understanding the world and developing innovation (Veblen 1914).

pharmaceutical knowledge structure. While dominant corporations can usually influence the substance of the regulatory framework according to their interests, political imperatives have sometimes forced the implementation of unwelcome measures for dominant interests (e.g. the implementation of tighter RCTs after the thalidomide scandal in 1962).

3- External factors: Wars, emergency measures, financial crashes and political imperatives were all causal factors in the transformation of how Big Pharma shaped and controlled the pharmaceutical knowledge structure. The First World War, for example, allowed the United States to appropriate German patents and to partly develop America's dominance in chemicals and pharmaceuticals.

This chapter relates Big Pharma's history in four parts: First, it relates how this business sector emerged under the dominance of German firms and cartels. Second, it explains how American firms managed to develop in a sector controlled by foreign interests before the Second World War. The analysis particularly shows how cartels and patents were the main business devices to build important monopolistic capacities and intangible assets for dominant firms. The third part focuses on the American made business model that emerged in the 1950s with the conjunction of the therapeutic revolution and the marketing revolution. The analysis shows how this new business model reshaped the GPB and reorganized completely the knowledge structure. The business model evolved in the 1960s and 1970s because of both the end of the therapeutic revolution and the implementation of systematic randomized clinical trials (RCTs). The analysis explains in what way RCTs became central to today's GPB, and how they constitute the core of the knowledge structure controlled by Big Pharma. The chapter concludes on the (perceived) bad shape of the competitiveness of the American Pharmaceutical Business at the end of the 1970s with the revivals of generics

and the globalization process from which emerged important competitors to American firms. Those perceived challenges to American dominance are the necessary starting points to understand the institutional reactions that brought important transformations in the power structures of the GPB in the 1980s, and gave rise to the knowledge-based economy. Those institutional reactions will be explored in the next chapters.

4.1 From Origins to German Dominance

The history of Big Pharma began with the birth of corporate capitalism; that is the institutional reorganization of ownership structures, from which the large corporations that shaped the twentieth century arose. The modern pharmaceutical business emerged in the 1880s, during what historians call the "Second Industrial Revolution". The First Industrial Revolution began in late eighteenth century with coal-powered machinery that allowed the emergence of large manufacturing facilities. The Second Industrial Revolution, in the late nineteenth century, was based on the emergence of mass transportation and communication (coal-powered locomotives, steamships, telegraph and telephone infrastructures) that facilitated mass production and mass distribution to national and worldwide markets. The great industrial efficiency that resulted from such technological developments brought about transformations in the institutional forms of ownership. In fact, business sectors adapted to this industrial revolution by forming corporations, pools, trusts and holdings. Such institutional forms allowed preventing overproduction, which would result in falling profits (Roy 1997).

The first corporations to capture the main technologies to produce pharmaceuticals and to develop their business efficiency accordingly became the core companies embodying Big Pharma. These first movers created barriers to entry to their select club. The history of Big Pharma thus became the history of corporations fighting for dominance in the pharmaceutical market in order to move behind or remain inside the barriers to entry.

The Emergence of a Business Sector

The modern pharmaceutical industry was born in the second half of the nineteenth century with the development of extractive and synthetic chemistry. Before that, traditional medicines were based on the knowledge of plants and their effects on the human body. Hippocrates, the father of medicine in the fifth century B.C., recognized properties of different plants for their laxative, diuretic or narcotic effects. Galen, a Greek physician working for the Roman Emperor Marcus Aurelius from 160 to 180 A.D., codified the use of plants and conceived almost all Western traditional pharmaceutical formulas, which remained the basic reference for all physicians for 1600 years (Juès 1998). In the seventeenth Century, modern clinical medicine emerged with Harvey's discovery of blood circulation and Sydenham's nosological method of classifying diseases (Gingras et al. 1998). While the medical practice evolved, the cupboard of specific pharmaceutical remedies remained desperately bare. The modern pharmacopoeia emerged in the nineteenth century with the isolation of active ingredients in plants, thanks to the progress of the chemical industry, especially in alkaloids and organic acids.

After the isolation of morphine from opium in 1806, followed in succession the isolation of strychnine, quinine, caffeine, codeine and salicyline, from which Bayer later produced

Aspirin (Juès 1998, 5-8). Isolated active ingredients were now pure, well defined and somewhat easy to produce once chemists knew what they were looking for. It was now possible to associate clearly the active ingredients with their effects on the human body and to measure precisely the dosage for best efficacy. The invention of the hypodermic syringe in the same years also had a great impact in the formation of this new type of pharmaceutical research, allowing research for serums and vaccines. This ability to test pure substances directly in the human body opened the way to new forms of pharmaceutical research with a rational approach to the nature and effects of compounds. The old apothecary's dispensary became outdated; to obtain the new remedies, pharmacists started to rely on pharmaceutical research laboratories.

A typical pharmaceutical company that emerged at this time was John K. Smith and Co. (later part of GlaxoSmithKline). Established in 1841 in Philadelphia, a city where the selling of pharmaceuticals was often a physician's sideline, John K. Smith and Co. developed by manufacturing and distributing precisely measured drugs to physicians (Liebenau 1987, 11-18). Another typical company of that time was Merck, a German apothecary business founded in 1668 and transformed in 1827 into a drug manufacturer. Its first products were morphine, codeine and cocaine (Derdak 1995, 289). During the second half of the nineteenth century, the pharmaceutical research laboratories, allowing greater specialization and production drifted away from traditional pharmacies to become industrial enterprises. Military demand, among others, allowed small manufacturers like E.R. Squibb (later part of Bristol-Myers-Squibb) or Wyeth to become large drug manufacturers (Liebenau 1987, 18-20). It was in Continental Europe, however, that the main pharmaceutical business structures emerged.

The first alkaloid drugs, based on plants extracts, were achieved through chemical processes that were already being used to obtain dyes. In fact, the first important pharmaceutical businesses appeared in cities where the production of dyes was a local specialty. For example, the first Swiss pharmaceutical businesses were linked to dyestuff manufacturers for the famous silk industry in Basel. Swiss companies that came to dominate the pharmaceutical business, Geigy, Ciba, Sandoz and F. Hoffman-La Roche[54] (the first three are now part of Novartis, and the last one is now Roche), were all based in Basel and were linked to dyestuff manufacturing. In the same way, in France, La Société Chimique des Usines du Rhône (later part of Rhone-Poulenc, which is now part of Sanofi-Aventis) developed its expertise by producing dyes for Lyon's renowned silk industry.

The discovery of the first synthetic dyestuff in 1856 opened the way to large-scale production using new techniques. In 1880, three German firms began to commercialize the first manmade dyes and became world leaders in dyestuff manufacturing: Bayer, BASF and Hoechst (now part of Sanofi-Aventis). All based on the banks of the Rhine River, they built their integrated learning-bases in the 1880s and 1890s by establishing the new industrial organic chemical industry. Bayer administered the lower Rhine territory, Hoechst the middle Rhine and BASF the upper Rhine. They created the world's first large-scale industrial laboratories, highly organized and specialized, improving existing processes and creating new ones. Large plants covered hundreds of acres on the Rhine River where they benefited from the cheap coal available in the region and they developed an impressive system of mass production. At the same time, in order to sell their new products in Europe, America and

[54] Note that F. Hoffman-La Roche was not exactly a dyestuff manufacturer that evolved into a pharmaceutical company. It was F. Hoffman-La Roche's father, a wealthy silk merchant who founded a pharmaceutical company for his son who showed an interest in entrepreneurship (Derdak 2003, 190).

Asia, those three firms developed important marketing organizations in order to "teach" customers how to use their synthetic dyes as compared to older natural dyes (Chandler 2005, 114-118). The first movers in the GPB were thus Germans.

Cartels and Patents; Core of German Dominance

Cartels and patents were central in the emergence and consolidation of the early GPB. The German chemical firms came to dominate the international production of chemicals and, consequently, of pharmaceuticals before the First World War. German firms benefited from two major advantages: 1) a state encouragement of cartels for better competitive advantage and to end destructive free competition[55] (Levy [1935] 2001); and 2) the development of an organized patent system as early as 1877 that allowed German firms to build important barriers to entry around their industrial sector.

Cartelization was central to the German firms' strategy for maximizing their world market shares. Cartels, sometimes called pools, are horizontal cooperation agreements between formally independent firms in order to restrain competition by implementing production quotas, fixing prices, distributing market shares or pooling profits. In 1904, Bayer, AGFA and BASF formed *Interessengemeinschaft* (I.G.), which was a community of interest with pooled profits. Carl Duisberg, the director of BASF and founder of I.G., predicted that I.G. would emerge as a true "state within the state" (Stocking and Watkins 1946, 414). Non-chemical firms producing only pharmaceuticals also formed their own

[55] At the time, the German Historical School dominated all chairs in political economy in Germany and economists of this school, such as Kleinwachter or Schaeffle, saw industrial combination as a solution to free competition, which would inevitably end up in anarchy. In the same way, radical economists like Hilferding or Schönlank saw cartelization as a movement towards general socialization.

cartel, Pharma I.G. in 1905 (Wengenroth 1997, 144). Before the First World War, however, chemical firms remained the leaders in discovering new pharmaceutical compounds, and they remained the core companies in pharmaceuticals. In 1907, Hoechst created its own community of interest with two other major chemical firms: Cassella and Kalle. Under the pressure of the First World War, the group led by Hoechst joined, together with the electrochemical producer Greisheim Elektron, with I.G. in 1916. All those chemical firms thus formed a single I.G. with important intangible assets based on their impressive political power (Chandler 2005, 117). For example, an American businessman in Germany wrote at the time (quoted in Stocking and Watkins 1946, 414n): "Six weeks in Germany have convinced me that I.G. is the real octopus embracing almost everything in the economic, and a large part of the political, life of post-war Germany. Whenever you mention the name of I.G. to anybody in Germany, he registers awe, fear, admiration..." When chemists at Bayer (then part of I.G.) discovered in 1921 a new compound for curing African sleeping sickness, which was a real plague in British colonies, Bayer offered the British the formula of the drug, patriotically called *Germanin*, in exchange for African colonies. Britain declined (Derdak 1996, 75).

In order to remove any remnant of competition, all those firms that had been pooling their profits agreed to merge into a single entity in 1925 to form the giant I.G. Farben. The power of that firm, in which Bayer was the most important player, cannot be understated. Their high capitalization was based on their monopolistic capacities and their political power. In addition to setting quotas and rising prices, I.G. Farben pursued the political aims of preventing leftist movements from taking control of the industry by financing right-wing politicians and by influencing domestic policies through secret meetings with German

leaders. I.G. Farben contributed to the rise of the Nazi party domestically and they also contributed an estimated 10 million marks to Nazi associations abroad. Historical records show that such investment was worth every penny (Derdak 1996, 75):

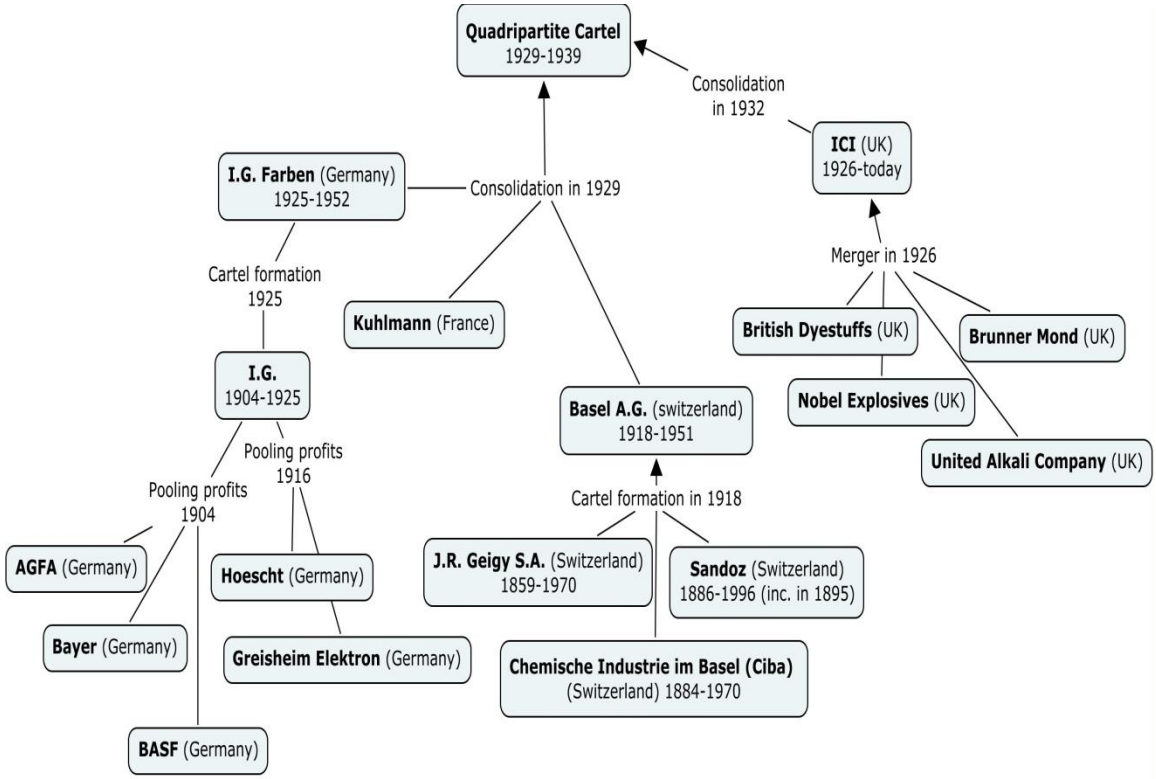
> Bayer and I.G. Farben profited handsomely from their support of Adolf Hitler. By 1942, the I.G. Farben was making a yearly profit of 800 million marks more than its entire combined capitalization in 1925, the year the cartel was formalized. Not only was the I.G. Farben given possession of chemical companies in foreign lands (the I.G. Farben had control of Czechoslovakian dye works a week after the Nazi invasion), but the captured lands provided its factories in Germany with slave labor. In order to take full advantage of slave labor, I.G. Farben plants were built next to Maidanek and Auschwitz.

The cartelization of the chemical business in Germany brought other national chemical businesses to favor cartelization. Such was the case in Switzerland. At first, the Swiss chemical firms in Basel were only a part of the supporting nexus for dominant German firms, which dominated the world dye trade with a 90% world market share. German chemical firms had a vested interest, however, in the survival of their Swiss counterparts since 80% of the raw materials used by Swiss firms were bought from Germany (Derdak 2001, 304-5). The First World War, which drove German products out of different markets in Europe, America and Asia, presented the Swiss chemical manufacturers with a great opportunity. Unable to obtain their needed raw materials from Germany, Swiss firms formed a joint venture with British firms, obtaining their raw materials from Britain in exchange of supplying the British markets with dyestuff, which the British previously had obtained primarily from German firms. The Swiss firms thus managed to create an important production capacity filling the European markets now closed to German suppliers. The most important Swiss chemical firm, Ciba, saw its profits grow from SFr 3 million in 1913 to SFr 15 million in 1917. After the World War, however, with the Swiss and German firms both

able to supply all European needs, the chemical business was in a state of severe overcapacity, which brought Ciba profits down to SFr 1 million (Derdak 2001, 305).

German chemical firms remained dominant, but invited the Swiss firms to join their cartel. In order to remain independent, all Basel chemical firms, which mean almost all Swiss chemical firms, chose to create their own cartel: Basel AG, comprising Ciba, Geigy and Sandoz. Placing profit before independence, Basel AG joined I.G. Farben in 1929 to create the giant Dual Cartel. French dye makers also formed a syndicate, led by Kuhlmann, and joined shortly thereafter the Dual Cartel to create the Tripartite Cartel (Lacroix-Riz 2002). The British chemical sector created its own cartel in 1926, ICI, regrouping Brunner, Mond, Billingham, United Alkali, British Dyestuff and Nobel Industries (Chandler 2005, 127-9). In 1932, ICI joined the Tripartite Cartel, which became a pan-European entity renamed the Quadripartite cartel, sometimes also called the European dye cartel (Derdak 2001, 305). Figure 4.1 synthesizes this cartelization movement in European dyestuff chemicals before the Second World War.

Figure 4.1: Genealogy of the Quadripartite Cartel (European dye cartel)



Sources: Lacroix-Riz 2002; Chandler 2005; Derdak (various years).

This pan-European cartel in chemicals remained active until World War II, which forced its dissolution. This cartel in dyestuffs was only one among many that organized the global productive forces of the chemical industry in such a way as to avoid overproduction and maintain high profits in the global markets. Analyzing the "global market" for chemicals and pharmaceuticals, the magazine *Fortune* arrived at the same conclusion that this "market" was consciously planned and organized for the benefits of a few firms (Fortune 1937, 157, 162):

> The chemical industry, despite its slowly lowering curve of real prices, is an "orderly" industry. It was practicing "cooperation" long before General Johnson invented it in 1933. It has seldom been bedeviled by overproduction, has had no private depressions of its own, and has not often involved itself in long bloody price wars. [...] By and large the chemical industry has regulated itself in a manner that would please even a Soviet Commissar [...] The industry [is] the practitioner of one definite sort of planned economy.
> Today the whole chemical picture has an air of financial stability that is unusual in so new an industry. There is no evidence of fighting among its companies for position: price structures are steady [...] and it will continue to be: new developments seek outlets through established chemical industrial channels, for there lie the talent and the money for development, one as vital as the other for any new process.

Patents were also central to the process of cartelization and industrial combination in Germany (Kronstein 1942). The difficulty of producing anything without constant access to full knowledge and the threat of "mutually assured patent litigations" forced cooperation between the firms and dictated strategies for pooled profits, cartels or combinations. In a book published in 1923 and titled *Die Patent Gemenschaft in Dienst des Kartellgedankens*, Hermann Isay observed (quoted in Hexner 1946, 72): "No other industries have at their disposal for cartelizing purposes as effective a device as the manufacturing industries have. This auxiliary device is the patent". The German chemical business employed thousands of chemists, whose output was measured by the issuance of thousands of patents (Drahos & Braithwaite 2002, 47). Although Germany granted only process patents, German patent law benefited patent *applicants* instead of *inventors*, thereby allowing firms to claim patent rights over their employees' innovations (May & Sell 2006, 127). The German firms also benefited strongly from the U.S. and British patent systems that allowed product patents, which created colossal barriers to the development of their national industry.

Patents had another important benefit for the newborn German business organizations: legal expertise. Officially, innovative firms must divulge their industrial information in order to obtain a patent, which benefits competitors as soon as the patent expires. German firms

were the first to set up patent departments, which brought them important legal expertise on how to obtain very general patents (thereby broadening barriers to entry) while divulging very little information. In the United States, for example, German chemical companies, such as Bayer and BASF, wove webs of hundreds of patents, creating a "colossal obstacle to the development of the American dyestuff industry" (Greenberg 1926-1927, 19-20). In 1912, according to a study of the U.S. Tariff Board, 98% of applications for patents in the chemical field had been assigned to German firms and were never worked in the United States (Noble 1977, 16).

German expertise in drafting patents in such a way as to hide important information was evident during the First World War. Although, the Western allies confiscated many German patents, they were of little use since German firms kept careful control over their know-how. British, U.S. and French chemical industries were usually incapable of working the seized patents. It is not surprising, according to William Pope, a Cambridge University chemistry professor writing in 1917 (Pope 1917, 18):

> The Bayer Company, like the other German fine chemical firms, holds many thousands of carefully drawn patents (...) it must be understood that many of these patents are bogus, that is to say, contain deliberate misstatements for the purpose of misleading inquiring minds as to the manner in which important products are manufactured by the firm. In fact, some German patents are drawn for the purpose of discouraging investigation by more practical methods; thus, any one who attempted to repeat the method of manufacturing a dye stuff protected by Salzmann and Krüger in the German Patent No. 12096 would be pretty certain to kill himself during the operation.

German firms surely developed an important productive capacity in chemicals, but the assets at the basis of their capitalization were mostly intangible. With a cartelized business sector to organize production and distribution, a web of defensive patents stifling competition

and a legal expertise to preserve their know-how, the dominance of German firms seemed, at the time, impossible to overthrow.

4.2 The Rise of the American Challengers

In the United States, most firms embodying today's American Big Pharma appeared in the nineteenth century. As discussed above, the pharmaceutical knowledge structure before the First World War was first and foremost dominated by German firms, which owned most of the patents at the time. It has also been shown, however, that American firms hold today's bulk of capitalization in pharmaceuticals, which translates into greater earning-capacity through greater control. The history of the GPB in the twentieth century is thus the history of the shift from German to American dominance.

Such shift was possible not because American pharmaceutical firms managed to develop greater productive capacities in a competitive market environment, but, instead, because it managed to develop an institutional structure offering such monopolistic capacities to its firms that they were able to cross the barriers to entry set up by German dominance. Besides, the two world wars, lost by Germany, offered opportunities to American firms to become themselves core companies. This section introduces first the favorable institutional structure put in place in the United States that allowed cartelization through patents, and then explain the different paths by which American pharmaceutical firms managed to evolve into dominant firms in the GPB.

The American Monopoly Game

In the United States, there was no state encouragement of cartels and antitrust statutes were put in place in order to prevent too vast business concentration. Patenting, however, came to replace cartels as the institutional form to restrain competition in the American twentieth century. During the nineteenth century, pools and trusts were a very common device for business combination in different business sectors in the United States. For economists of the time, such combinations were considered beneficial since, like medieval guilds, it was a device to restrain the perceived evils of too much market competition. As the neoclassical economist John Bates Clark (1887, 55) puts it:

> Combinations have their roots in the nature of social industry and are normal in their origin, their development, and their practical working. They are neither to be deprecated by scientists nor suppressed by legislators. They are the result of an evolution, and are the happy outcome of a competition so abnormal that the continuance of it would have meant widespread ruin.

Pools have been, for a long time, the main way to restrain competition. In his study of pools and trusts, William Z. Ripley (1905, xiii) explains: "The pool is probably the oldest, the most common and at the same time the most popular, mode of obviating the evils of competition". The pool socializes business control over an industry's collective output, but its enforcement is not necessarily guaranteed because of free-riders (Roy 1997, 183-184):

> Producers agree to collectively set output levels and prices, sometimes turning over their product to a central distributing organization, at other times paying a fee to a coordinating agency that fines any firm that deviates from the collective agreement. However, if the contributions that firms make to the collective fund are less than the profit from violating the output and price agreements, pools are very difficult to sustain unless governments are willing to enforce the contracts that constitute them.

In the mid-nineteenth century, pools were frequent in regional areas, where producers of the same local business community passed agreements about how to organize production and distribution in different sectors. The influence of the local business community on local authorities was enough to maintain pool agreements, even if existing statutes made it illegal. The social impacts of pools did not become a public issue until the second industrial revolution; that is, with the emergence of mass transportation and mass communication that permitted organization of production and distribution at a national level. The national scope of industry during the second half of the nineteenth century eroded local and regional arrangements. Whereas Germany encouraged and enforced cooperation agreements (kartells) in different sectors, this was not the case in the United States where common law generally invalidated agreements to fix prices and restrain trade[56]. While American businessmen in many industries nevertheless attempted to create pools on a national scale, they lacked the precondition for success, which was the legal support and tight social organization they enjoyed at the local level. With the rise of corporations in the United States as the legal structure controlling the productive forces, the new form of business combination favored by American businessmen became the trust. Davies (1916, 7) explains the origins of the trust:

> The trust was an ancient device by which the legal ownership and management of property could be put in the hands of one person (trustee) while the beneficial interest remained in another person (cestui que trust). [...] The first application of this device for the purpose of forming a combination to control the market is attributed to Standard Oil Co [in 1879]. Before 1879 this combination had been held together very largely by means of exchanging the stock of other companies.

[56] For a discussion of the decisions made in the United States under the common law covering various forms of business combinations, see Davies (1916, 24-73).

Trust combinations were of considerable magnitude in the United States and, because of the interstate scope of their commerce, states' legislation against the abuse of power in business combinations became ineffective. The federal government thus decided to intervene, first with the Interstate Commerce Act of 1887, and then with the Sherman Antitrust Act of 1890. Those pieces of legislation were nevertheless ineffective. In 1895, in the Knight Case, the U.S. Supreme Court made a distinction between "manufacturing" and "commerce", holding that the Antitrust Act did not apply to combinations or consolidations of manufacturing establishments (Davies 1916, 11). While there was a rapid growth of trusts between 1898 and 1901, this form of business combination remained on the border of illegality and could face fines under different state statutes. The holding company, a company holding the majority of outstanding stocks of other companies, became the new business attempt as a means to obtain monopolistic control over the industry. A Supreme Court decision in 1904 (the Northern Securities Case), however, forced the dissolution of an important holding company in railroads under the Sherman Antitrust Act, and thus slowed down this form of business combination. The Clayton Antitrust Act of 1914 put an end to holding company as a device for monopolization since it prohibited "the holding by one company of the stock of another company" (quoted in Davies 1916, 22). The struggle by American businessmen to increase their profits through business combination and monopolistic control was thus constantly defied by new antitrust legislation. Direct business combinations to create monopolies were often subject to the scrutiny of courts. A new solution to provide businessmen greater monopolistic capacities was offered in the beginning of the twentieth century: Patents.

Patents: Highest Stage of Business Combinations

The U.S. Patent Act of 1836 put in place the foundation of the present American patent system, which includes the examination of each patent application. Based on the Founding Fathers' concept that government must feed the fire of genius with the fuel of interest (Noble 1977, 87), the system stimulated individuals by rewarding their creativity and ingenuity with property rights over the fruits of their intellectual labor. Most patents were thus granted to individual inventors. Some corporations, however, began to develop patent strategies in the 1880s as a form of business control over the industry and the market (May and Sell 2006, 122-4). After making sure, by contract, that any invention by their employees in their research laboratories would belong to the corporation[57], firms like AT&T, GE, Westinghouse and the Edison and Swan Electric Light Company managed to develop impressive patent portfolios that granted them important control over their business sector. In fact, the recourse by corporations to patents as a means to develop monopolistic capacities was encouraged by patent lawyers in order to increase their clientele (Drahos and Braithwaite 2002, 43):

> This technical knowledge, along with the procedural intricacies of obtaining patents, allowed the [patent] profession over time to acquire enormous technocratic power, a power that was obscured by the mind-numbing technicality of patent "lore". It was they who devised the patent strategies that served corporations playing the knowledge game. It was they who campaigned for "reform" of the patent system. It was they who would, as the astute lackeys of the industrial research system, tilt, over a period of decades, the patent system in favor of private interests at the expense of the public interest.

[57] Transferring the responsibility of invention from the individuals to corporations is a subversion of the intent of the patent system that the patent profession was well aware of, but encouraged anyway. See Noble (1977, 90).

A most influential institutional entrepreneur of the patent profession was Edwin J. Prindle, a mechanical engineer and patent lawyer who became the president of the *New York Patent Law Association*. Prindle was a fierce advocate of patents for corporations, and went door to door to convince corporations about the great opportunities about how patents could help them develop their intangible assets. In 1906, Prindle wrote a widely-read series in *Engineering Magazine*, entitled "Patents as a Factor in a Manufacturing Business", in which he explained the opportunities that patents offered for market monopoly (quoted in Noble 1977, 89):

> Patents are the best and most effective means of controlling competition. They occasionally give absolute command of the market, enabling their owner to name the price without regard to cost of production [...] Patents are the only legal form of absolute monopoly. [...]
> The power which a patentee has to dictate the conditions under which his monopoly may be exercised has been used to form trade agreements throughout practically entire industries, and if the purpose of the combination is primarily to secure benefit from the patent monopoly, the combination is legitimate. Under such combinations there can be effective agreements as to prices to be maintained [...]; the output for each member of the combination can be specified and enforced [...] and many other benefits which were sought to be secured by trade combinations made by simple agreements can be added. Such trade combinations under patents are the only valid and enforceable trade combinations that can be made in the United States.

The series continued in the same vein, stressing the best strategies for corporations to develop the strongest monopolistic capacity through patents. Prindle's claims are typical of the emerging idea that patents had to be used to control markets and increase monopolization, rather than as a device for the public good of supporting innovation. Following the advice of the patent profession, the corporate race to build patent portfolios began at the turn of the twentieth century. From 1836 to 1870, the number of patents issued was 120,573. In 1911, that number had jumped to 1,002,478 (Drahos and Braithwaite 2002,

47). In 1885, 12% of patents were issued to corporations; by 1950 at least 75% were assigned to corporations (Noble 1977, 87).

Research-based corporations struggled to obtain as many patents as possible for three reasons. First, raising patent thickets enabled patent-holding companies to build important barriers to entry in their respective business sectors. Second, since most business sectors are arenas for more than one player, developing strong patent portfolio enabled firms to obtain strong bargaining positions when cross-licensing their patents with competitors. Third, cross-licensing patents allow the possibility of business cartelization in order to raise prices, fix quotas and divide world markets.

As claimed by Prindle, patent pools became a very common way to create informal cartels. In contrast with pools and cartels of the nineteenth century, the patent cartels were now enforced by the state, since a breach of cartel agreements was a breach of patent law, and the state was called upon to intervene to protect the cartel. Cartels, in their legal patent form, were not illegal anymore, and the problem of dishonest individual cartel members (free-riders) that impeded coherent national cartelization of the U.S. economy was now solved. For all these reasons, patents quickly became central as a business instrument to control the industry and develop the firm's intangible assets. Stocking and Watkins (1946, 429) describes the patent game as follows for the chemical industry:

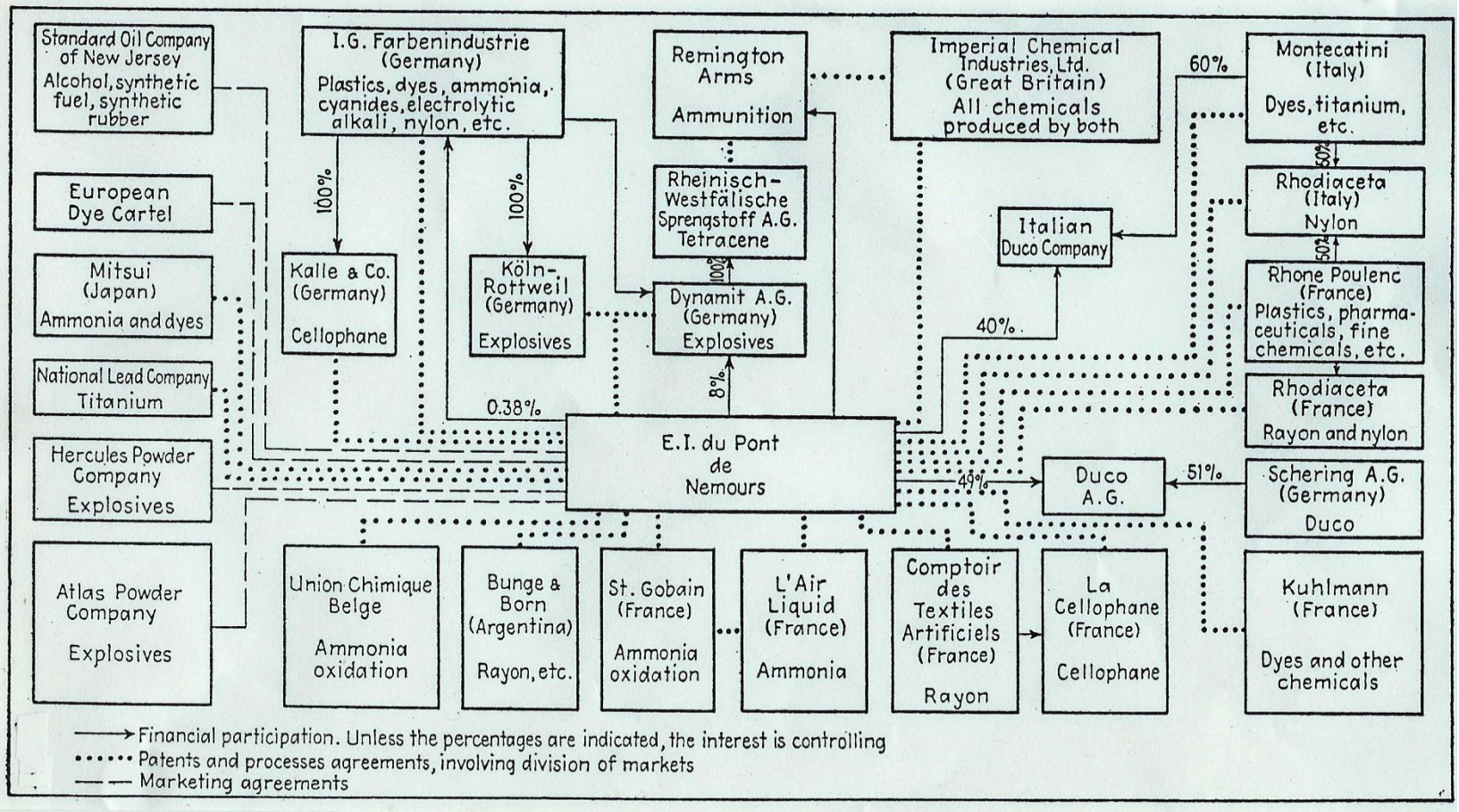
> In their intercorporate dealings, large and powerful chemical companies use patents and secret processes as counters in a never-ending bargaining process. They "swap" them for equivalent benefits from others. They trade them for the right to a larger share in existing markets or for participation in new fields. They use them as chips in a poker game in which the stakes are the world markets. While patents and "know-how" may promote the industrial arts, they also are unquestionably a source of business power.

The use of patents to structure and enforce cartels, formal or informal, spread between the two world wars. According to Stocking and Watkins (1946, 4), cartels became the "outstanding characteristic of business", and, according to their case studies, patents agreements over products or processes have been the main way to divide world market shares between corporate entities. For example, the authors analyze the building of monopolistic power by DuPont, the American dominant firm in chemicals. DuPont, founded in 1802, focused only on explosives until it embarked on a program of "trust building" in the 1890s. By 1912, DuPont had absorbed a hundred other explosives companies, achieving almost a complete monopoly, and diversified into other chemicals (Stocking and Watkins 1946, 381). The First World War provided huge windfall profits for DuPont, which benefited also from the expropriation of German patents and the liberation of Allied markets. According to DuPont's corporate website (DuPont Heritage 2003), those favorable events allowed DuPont to diversify its production in other types of chemicals, financing its expansion by advance payments on Allied munitions contracts. Between the two wars, DuPont wove a large web of cartel connections with the 21 business entities that controlled the major markets in which DuPont had interests. A typical agreement was a signed pact with a competitor in order to share patents, information and to divide the international market according to the best of their interests, just as in the case of the alliance between DuPont and the British ICI, as described on their website (DuPont Heritage 2003):

> In the late 1920s DuPont's commitment to intensive, long-range research and product diversification placed it in direct competition with powerful European combines like Britain's recently formed Imperial Chemical Industries. DuPont and ICI agreed in October 1929 to share information about patents and research developments. The firms also agreed not to compete in certain geographical territories and established successful joint ventures in Canada, Argentina and Brazil.

Analyzing in depth Dupont's international cartel connections between 1934 and 1939, Stocking and Watkins (1946) showed that, in fact, 70% of the cartel agreements were based on patent agreements over products or processes (see figure 4.2). DuPont thus provides an important example that, in manufacturing sectors like chemicals and pharmaceuticals, patents agreements were the main strategy to build monopolistic power, control the industry and develop intangible assets. Patents were central to cartels, formal or informal, that reigned supreme in the world economy. Between the two world wars, no American pharmaceutical firms, however, would become as important as chemical firms such as DuPont and Union Carbide. But some American pharmaceutical firms slowly became more and more important between the two wars, competing with German firms, to finally rise to dominance with the Second World War.

Figure 4.2: DuPont's Major International Cartel Agreements (1934-1939)



Source: Stocking and Watkins (1946, 464)

American Paths to Pharmaceutical Success

The first movers that managed to become core pharmaceutical companies among American firms succeed by following different paths: By focusing on R&D, by focusing on marketing, or by finding an equilibrated combination of the two. The marketing path has been the natural path for American firms because of German domination in R&D. Most American firms that managed to move behind the barriers to entry in pharmaceuticals before the Second World War, had done so by following the marketing path or by excelling in the OTC market. For those firms, the nature of competition was not to develop new products, but to control channels of distribution. Such was the case for marketing machines such as Warner-Lambert (now part of Pfizer), Upjohn (now part of Pharmacia and then Pfizer), Bristol-Myers (now part of Bristol-Myers Squibb), American Home Products (AHP, now called Wyeth), Johnson and Johnson (J&J) and Procter and Gamble. For example, William R. Warner, who founded in 1886 the company that would become Warner-Lambert, developed his company and earned his fortune by inventing sugar coating for pills. Dr. W.E. Upjohn, who founded Upjohn in 1896, discovered a way to produce friable pills that disintegrated rapidly into the body, and based its selling on the "pleasant taste" of its products (Siegelman 1996, 23). Bristol-Myers was set up in 1887 by two "detail men" and focused on direct-to-consumers advertising. AHP, established in 1926, has been a marketing-machine conglomerate that made its fortune by acquiring little-known products or companies at a reduced price, such as *Anacin* in 1930, and turning them into huge money-makers through aggressive advertising. J&J, established in 1886, first focused on health products, like bandages and sanitary napkins, and, late in the 1950s, managed to enter OTC and prescription drugs markets by acquiring smaller pharmaceutical firms and distributing their

products through their huge marketing capabilities. Procter & Gamble, established in 1837, is also a huge marketing machine just like AHP or J&J. It managed to overcome the barriers to entry of Big Pharma for some products but it is not considered a pharmaceutical firm, since pharmaceuticals retain only a small share of its revenues.

The R&D path has been a difficult one due to German dominance in chemistry and pharmaceuticals, with the involved patent thickets that goes with it. Due to the greater difficulty of the R&D path in America, firms that chose that path are less numerous than those that entered through marketing. It might not be a surprise that the secret of their success laid in part in their connections with German firms. Only three firms, which are now part of Big Pharma, can be considered to have made it through a path focused on R&D: Merck, Schering (now part of Schering-Plough) and Squibb (now part of Bristol-Myers Squibb). Merck and Schering were both subsidiaries of German firms producing and distributing German products in the United States since the 1880s. They became American dominant pharmaceutical firms when they were nationalized during the First World War, while retaining the expertise developed by its workers, researchers and managers. Squibb, established in 1858, managed to follow the R&D path when it was acquired in 1905 by Theodore Weicker. Weicker was a German chemist previously in charge of the American subsidiary of Merck. He chose to settle in the U.S. and to run his own company based on his own expertise and his business connections with German firms. Merck, Schering and Squibb all managed to make it through the R&D path thanks to their connections and networks with German producers and manufacturers. With time, however, those three had to make a move through mergers or acquisitions to also develop their marketing capabilities in order to enter and remain in the realm of Big Pharma.

Other American firms had a different path, they were born out of marketing but managed to quickly develop their own in-house R&D capabilities, especially during the First World War. Abbott Laboratories, Eli Lilly and Parke-Davis (now part of Pfizer) are three firms that followed that path. Abbott Laboratories began its activities in 1888 by marketing a new way to market drugs: Alkaloid pills or dosimetric granules. Champion in marketing, Abbott Laboratories developed its R&D capabilities during the First World War to substitute drugs manufactured exclusively by German companies that were no longer available in the United States (Derdak 2001, 9). Eli Lilly, established in 1876, enjoyed an important commercial success with its gelatin pill as a new way to market drugs. By hiring its first scientist in 1886, Eli Lilly established one of the first pharmaceutical R&D program in the United States, and thus benefited greatly from the First World War, which opened markets to its products. Parke-Davis, established in 1871, obtained commercial success with the mass production of hard gelatin capsules and the launch of the first line of standardized preparations known to pharmacy (Siegelman 1996, 24). Parke-Davis then developed its R&D capabilities by setting up the first American full-scale research laboratory in 1902 and, as Eli Lilly, also benefited greatly from the First World War. Note that a smaller company, Sterling, also greatly benefited from the First World War by obtaining the seized U.S. assets of Bayer, but also Bayer's trademarks, such as Aspirin, from the English Board of Trade. After the First World War, Bayer and I.G. Farben were thus forced to bargain with Sterling in order to re-enter the North and South American markets with their own trademark.

In spite of the formation of these important American corporations focusing on pharmaceuticals, it remains a bit far-fetched to consider that those firms really became dominant global companies before the Second World War. Some American leaders appeared

in the 1920s by embarking into wide-ranging pharmaceutical research, like Abbott Laboratories, Squibb, Parke-Davis or Eli Lilly (Noble 1977, 118), but they remained small players in the world business. Two main reasons can be identified for that situation. First, American pharmaceutical firms were focusing on pharmaceutical products, a sub-class of the chemical industry, while German firms producing pharmaceuticals were full-scale chemical firms. For example, in 1937, the U.S. production of pharmaceuticals represented only $335 million in the $2.6 billion chemical business (U.S. Department of Commerce 1939, 816-819). Before the Second World War, no pharmaceutical firm in America grew as large as the American core chemical firms like DuPont, Union Carbide or Allied Chemical and Dye Corporation (later named Honeywell), which together accounted for 66% of all tangible assets of the American chemical industry in 1935 (Rochester 1936, 193-195). American Cyanamid, which bought 35 companies between the two wars to slowly change its focus from fertilizers to dyestuff and pharmaceuticals, also deserves mention as a giant of the chemical business (Stocking and Watkins 1946, 385-386). A second reason for the moderate size of U.S. pharmaceutical firms is that German patents and cartels remained the main barriers to entry in spite of the First World War that opened the door to some American firms. In 1938, Germany reigned supreme in terms of exports in pharmaceuticals and medicaments.[58] As shown in Table 4.1, Germany, UK, France, Switzerland and USA represented together between 80-90% of world exports, and Germany alone represented the bulk of it.

[58] Pharmaceuticals include bulk pharmaceuticals while the word "medicament" designates finished pharmaceutical products in dosage forms and retail packs.

Table 4.1: Share of World Trade in Pharmaceuticals and Medicaments in 1938

(Between Top 5 Countries, % by Value)

Countries	Exports in Pharmaceuticals	Exports in Medicaments
Germany	44	59
UK	15	10
France	14	8
Switzerland	11	10
USA	16	13
Combined 5 countries	**100**	**100**

Source: Redwood (1987, 38-41)

Those elements, however, were about to dissolve with the therapeutic revolution that began during the Second World War, and the marketing revolution that quickly followed. The American dominance was about to emerge.

4.3 Time of Revolutions: A New Knowledge Structure

The Second World War marked the emergence of American pharmaceutical core companies at the heart of the GPB. The French and German pharmaceutical businesses were greatly disrupted by the war while the American pharmaceutical industry remained unscathed and was even reinforced because of the crash war programs put in place by the American government to help companies in developing new drugs. The seizing of German assets and patents in the U.S. and the military demand for medicines also served the growth of

American firms. The shift to American dominance, however, happened mostly through what Temin (1980, 58) calls "the therapeutic revolution". Combined with a marketing revolution that quickly followed, the therapeutic revolution entirely reorganized the knowledge structure in pharmaceuticals and allowed the emergence of a new business model, in which American and Swiss firms were the first movers. The therapeutic revolution is the act of birth of modern Big Pharma. However, this revolution ended in the 1960s, as began a regulatory revolution that tightened safety regulations and pushed further the transformation of the whole knowledge structure by implementing modern Randomized Clinical Trials (RCTs).

The Therapeutic Revolution

In the early 1940s, the R&D efforts of American firms were enhanced with different government programs to promote R&D for the needs of the war. In the case of pharmaceuticals, those efforts led to a "cascade of discoveries" (Redwood 1987, 43). From the 1940s to the 1960s, the major part of the modern pharmacopoeia will appear on the pharmacist's shelves. Many of today's blockbusters are still improved versions of this generation of discoveries. Nevertheless, those discoveries were often made in spite of total ignorance of the biological mechanisms at work, and all new medicines marketed during those years were all more or less the product of serendipity (Pignarre 2003, 41).

One of the central reasons for the therapeutic revolution was the implementation of a new method of research called *screening*. This method, pejoratively dubbed "molecular roulette", refers to the systematic testing of synthesized molecules on biological targets in order to statistically analyze, without preconceptions or understanding of the mechanisms at work, the effects of the molecules. This trial and error process allows systematic

serendipitous discoveries; once we know the biological targets, we can test molecules until we can find a "magic bullet", which is a compound that acts in a desired way on a biological target (and *only* on that biological target). Bayer's chemists developed this method while looking for dyes with antibacterial effects, which led in 1935 to the discovery of *Prontosil*, a sulfa drug that could treat syphilis (Pignarre 2003, 41). Due to its success, the screening method was quickly used on a larger scale. As Redwood (1987, 43) explains:

> Companies began to collect thousands of soil samples for microorganisms in the search for new antibiotics, and to synthesize profusely 'around' the molecular structure of known active compounds in the hope of discovering still greater or different forms of activity. It was this very erring in the scientific dark, done with great systematic skill and perseverance on a flimsy theoretical base, which in practice led to unprecedented advances in new drugs.

Another reason for the therapeutic revolution was the implementation, in the United States, of the 1938 Federal Food, Drug and Cosmetic Act. Despite the existence of numerous drugs in the 1930s, drugs were mostly used to reduce symptoms and ease pain, rather than to treat or cure diseases (Temin 1979, 434). Other drugs launched on the market were sometimes simply dangerous to public health. The Act required companies to preregister new drugs in order to give the FDA an opportunity to discard unsafe drugs. The FDA also had to decide if the drug could be sold OTC or if a prescription from a medical doctor was necessary. The distinction between OTC and ethical drugs existed before the Act but any non-narcotic drug could previously be bought either way by consumers. The Act was making a clear split between two channels of distribution: OTC or prescription. The number of ethical drugs increased, and such drugs have an important characteristic: the effective demand does not come from individual consumers (patients), but from the medical

profession that prescribes medicines to patients. The demand for R_X drugs was driven by doctors who did not have to pay for the medicines and often did not even know the price of the drugs they prescribed. The result was to create a very inelastic effective demand for ethical drugs (Temin 1979, 434-435), which allowed drug companies to steeply increase their prices and their margins. R_X drugs quickly became a much more profitable market, with the additional condition that the drug had to be protected by a monopolistic device such as a patent. With a greater volume of ethical drugs prescribed with higher margins than OTC drugs, firms were thus greatly encouraged to leave OTC products for the lure of more profitable patent protected ethical drugs.

The therapeutic revolution began with the demonstration of the antibiotic properties of penicillin in 1940. The American government put in place important crash war programs to develop and manufacture penicillin and sulfa drugs, providing financing to U.S. drug firms in order to expand their R&D facilities (Chandler 2005, 33). Pfizer was a first mover in the production of penicillin but the compound was not patent protected since it was made out of a natural substance. Its production was thus the subject of fierce commercial rivalry. By 1944, 19 American companies were producing penicillin, each competing in terms of more productive process technologies in order to lower production costs. The price of penicillin dropped from $8700 a kilo in 1945 to $620 a kilo in 1950 (Temin 1979, 435).

Streptomycin, the first antibiotic after penicillin, was discovered in 1943 through the screening of soil samples, which brilliantly demonstrated the screening method's effectiveness. In the case of streptomycin, the Patent Office ruled that the chemical modifications to micro-organisms were such that it created a new product and that both the product and the process could be patented. Introduced commercially in 1946 by Merck,

streptomycin became, in 1948, the first antibiotic to be patented in the United States (Temin 1979, 436). With patented products, competition shifted from more effective manufacturing processes to the discovery and development of new products (Temin 1980, 66):

> The drug industry began to transform itself from a fairly typical manufacturing industry to one based on the continual progress of technical knowledge. This transformation involved the development of a new technology, the growth of a new industry structure, and the marked intensification of older marketing practices.

A "cascade of discoveries" (Redwood 1987, 43-44) followed during the next years. After penicillin and streptomycin to treat infection, thiamine and folic acid were introduced in 1946 to be used against anemia. In 1948, vitamin B-12 was discovered independently by both Glaxo and Merck. The first major tranquilizer, chlorpromazine, which brought a revolution in psychiatry (Le Fanu 1999, 60-72), was discovered by Rhône-Poulenc in 1949. Five important, but quite similar, broad-spectrum antibiotics were launched consecutively: Lederle (owned by American Cyanamid) launched Aureomycin in 1948, Parke-Davis launched Chloromycetin in 1949, Pfizer introduced Terramycin in 1950, erythromycin is introduced by Lilly and Abbott in 1952 and Pfizer introduced tetracycline in 1953. Merck launched cortisone in 1950 while hydrocortisone was introduced in 1952. The first anti-tuberculosis drug was discovered independently by Roche and Squibb in 1952 while in the same year Geigy launched phenylbutazone, the first important non-steroidal anti-inflammatory drug. The Salk polio vaccine was introduced in 1955. Schering's prednisone, which treats inflammatory diseases, was introduced the same year with Wyeth's meprobamate, which treats anxiety. Hoechst's tolbutamide, opening the way for a first generation of oral hypoglycemics, was discovered in 1956. In 1957, oral contraceptives were

introduced by Searle in the United States. The same year, Lilly introduced propoxyphene, an important analgesic under the brand of "Darvon", and Geigy discovered imipramine, the first tetracyclic antidepressant. Merck's chlorothiazide, the first in a new generation of diuretics, was launched in 1957, followed by Ciba's hydrochlorothiazide in 1959. In 1958, Roche discovered chlordiazepoxide, an important tranquilizer marketed as *Librium*, which also led to the discovery of diazepam, another tranquilizer marketed by Roche as *Valium*.

The therapeutic revolution transformed the pharmaceutical business by greatly enlarging the territory of the pharmacopoeia with the discovery of broad-spectrum antibiotics, tranquilizers, hypoglycemics, diuretics, corticosteroids, antidepressants, oral contraceptives and non-steroidal anti-inflammatory drugs. It also transformed the pharmaceutical business by introducing new methods of discovery and by transforming pharmaceutical firms from traditional manufacturing firms into R&D firms. Due to high margins and higher volumes of prescriptions for branded ethical drugs, American pharmaceutical business began to focus more and more on branded ethical drugs, instead of OTC or generics. By 1954, the ratio of OTC to ethical drugs (in value) had become 33% (Redwood 1987, 42), as compared to 143% in 1937 (U.S. Department of Commerce 1939, 819). Generics that represented 40% of all prescriptions in 1948 fell to 5% in 1965 (Redwood 1987, 11). Accordingly, expenditures in R&D rose sharply during the therapeutic revolution: From 1953 to 1960, a time of low inflation, the annual American R&D expenditure in pharmaceuticals rose from $67 million to $207 million (Redwood 1987, 76).

Not only were American firms the main participants in the therapeutic revolution, but they also managed to take the lead in the pharmaceutical sector during this revolution. By 1960, the United States was producing 52% of the $6,2 billion in medicaments produced in

the 13 OECD countries (Redwood 1987, 52). American pharmaceutical firms were the first movers in the emergence of a new business model that changed the face of pharmaceuticals. The therapeutic revolution shifted the focus of pharmaceutical firms from manufacturing to R&D. The industry was now focusing on the continual progress of pharmaceutical knowledge, instead of trying to obtain cheaper production process for bulk manufacturing. Another important aspect, which had little to do with the therapeutic dimension of pharmaceuticals, was also central in the transformation of the pharmaceutical sector: The rising importance of marketing.

The Marketing Revolution

As explained earlier, the 1938 Federal Food, Drug, and Cosmetic Act created two distinct channels of distribution between OTC drugs, bought directly by patients, and ethical drugs, prescribed by doctors. According to the 1938 Act, firms could distribute their drugs through the prescription channel on a voluntary basis. The Durham-Humphrey Act of 1951, revoked this voluntary basis: A drug had to be either ethical or OTC, and it was the FDA that had to decide which drug had to go through which channel. Ethical drugs were more profitable because of their price inelasticity since doctors were prescribing drugs they were not buying. For pharmaceutical firms, marketing their drugs directly to the medical profession was becoming necessary to benefit from this more profitable distribution channel. Advertising to doctors existed before the 1938 Act but it was almost entirely done through the popular press (Temin 1980, 83-84). The increased profitability for ethical drugs would soon make the returns on advertising to the medical profession worth every penny. Such importance of promotion and advertising brought the introduction of statistical auditing of

the influence of promotion over doctors' prescribing habits in the 1940s and the creation of pharmaceutical marketing intelligence firms, such as IMS Health, in the 1950s (Greene 2007, 743).

Some pharmaceutical firms chose not to develop important marketing capabilities, preferring the use of nonexclusive licenses to market their drugs through licensed drug selling companies in exchange of royalties. Those firms soon fell behind the ones that managed to develop their marketing capabilities and that became vertically integrated in order to control their own distribution. By having their own sales forces advertising their drugs directly to doctors, drug manufacturing companies did not have to share profits by licensing drugs to other companies. Also, the termination of nonexclusive licensing allowed drug firms to better utilize their patent rights, retaining monopoly over production and restricting output for larger monopoly profits. While those profits could also have been obtained by simply raising royalty fees on nonexclusive licenses, the control over production was essential in developing an important bargaining position with competitors: "Patent monopolies were in fact only memberships in an oligopoly or price-fixing cartel, advertising was an important determinant of market shares within the cartel" (Temin 1979, 440). For example, tetracycline, an antibiotic that has chemical affinities with Terramycin and Aureomycin, led to a series of patent litigations that was settled by the constitution of a patent pool for broad-spectrum antibiotics; allowing the formation of a cartel in antibiotics.

In such a context where one well-protected and well-marketed drug could become a money machine (a *blockbuster*), firms began to see their revenues and profits derived primarily from only a few drugs and, as a result, were very aggressive in advertising those products to doctors as a means to ensure commercial success. Different data illustrate how

the association of profits and revenues to a few specific drugs became central to firms' business model. Data compiled in the course of a federal suit against the broad-spectrum antibiotic cartel shows, for example, that Lederle, owned by American Cyanamid, had a 20% return on capital, which consisted entirely of profits on tetracycline, a product sold under cartel arrangement with other drug firms (Costello 1968, 40). In 1960, among other firms in the antibiotics cartel, 33% of Pfizer's sales came from terramycin and tetracycline, and 45% of the Parke-Davis' sales came from chloramphenicol (Temin 1979, 442). The same patterns emerged for drug firms not specializing in antibiotics. For example, when Roche had to disclose financial information to explain its pricing policies in 1973, the authorities found out that 42% of its revenues were attributable to the sale of its two anxiolytics, Valium and Librium (Derdak 2003, 192). According to Temin (1979, 442), the same pattern applied to Upjohn's cortisone, Merck's Diuril and Searle's birth-control pills. This pattern of product concentration remains core to the Big Pharma model. According to calculations by UNIDO in 1988, Glaxo, Squibb, SmithKline Beckman and ICI obtained around half of their pharmaceutical revenues from only one drug. Ballance et al. (1992, 110) confirm the trend:

> Most [of the world's leading pharmaceutical companies] derive the bulk of their pharmaceutical revenues from the sales of a single product. On average, 21 per cent of the pharmaceutical revenues earned by the top 25 firms came from the sales of a single product. The introduction of only one or two new products can result in a rearrangement in the world rankings and market shares of leading multinationals.

This concentration on a few products is understandable under monopolistic and oligopolistic competition. It could not be argued here that there were cartel arrangements in every therapeutic class, as there were for broad-spectrum antibiotics. However, it would also

be problematic to suggest that there was market competition among the players of Big Pharma. For example, analyzing the hearings before the *Subcommittee on Antitrust and Monopoly of the Senate Judiciary Committee* on the ethical drug business in 1960, Steele (1964, 202) concludes that oligopolistic or monopolistic patterns exist at least for antibiotics, corticosteroids hormone, tranquilizers and oral antidiabetics, representing together 42% of total ethical drugs sales. Also, computing prices for 308 drug products between 1949 and 1959, Markham (1964) shows than 50% of the drug prices did not change during this 10-year period. He concluded that "[t]his is a remarkable history of price inflexibility which cannot be explained by the stability of the supply-and-demand conditions" (Markham 1964, 170). Gardiner C. Means (1972), analyzing the evolution of the prices of 50 commodities in different sectors, showed that drug products like antibiotics, tranquilizers and cardiac glycosides did not conform to the expectation of standard neoclassical theory. Demonstrating that, in general, prices are administration-dominated rather than market-dominated, he shows that the central mechanism for standard economics, the market, does not apply to most commodities, including drugs.

To be sure, some competition remained among drug firms, but this was achieved mostly through innovation, by differentiating existing products, and by controlling channels of distribution. By combining monopoly production and intensive marketing, the GPB became a business centered on pushing a few commercially important drugs through huge marketing campaigns. Drug firms had given birth to the blockbuster model. During this period, however, structural competition for differential accumulation still involved the production of new drugs and therapeutic innovation.

The firm Pfizer best illustrates this important transformation in the American pharmaceutical business in relation to patents and marketing during the therapeutic revolution. Pfizer was established in New York in 1849. A chemical firm producing iodine and acids, it pioneered the production of citric acid and developed large-scale fermentation technology. Pfizer never meant to become a core company in pharmaceuticals, but circumstances decided otherwise. The discovery in 1940 at Oxford University (UK) that penicillin could be used as a medicine to treat infections led doctors to search out a production process for large quantities of high quality penicillin. This would involve complex procedure for fermentation. To find such a production process became an imperative with Nazi air raids in London, but the conditions for experimentation were difficult on the European continent due to war. Howard Florey of Oxford University, who just discovered the medical application for penicillin, came to the United States desperately seeking the help of American scientists and asking the U.S. government to mobilize its scientific resources to produce the drug. The government approached Pfizer for its expertise in fermentation. After some experiments, Pfizer managed to find a workable production process for penicillin and mass production began in 1944. Pfizer's penicillin arrived in Europe with the Allied forces on D-Day on the beaches of Normandy (Derdak 2001, 358-359). The fast rising competition in the unprotected penicillin market after the war resulted in severe price reductions. Pfizer was not vertically integrated and was producing bulk pharmaceuticals without marketing its own products, in contrast to more successful firms like Squibb which produced fewer bulk pharmaceuticals than Pfizer but was more profitable since it was packaging its products and was selling them directly to pharmacies and hospitals (Temin 1980, 66). The situation changed for Pfizer in 1950 with the discovery of

Terramycin, an important broad-spectrum antibiotic that Pfizer managed to discover thanks to its new expertise in the domain. Pfizer's new President John McKeen took the decision to leap forward in the realm of Big Pharma by marketing the drug under a Pfizer trademark. With a very small but growing salesforce, Pfizer was facing overloaded traditional marketing channels due to competitors' important promotional expenditures. Pfizer managed to circumvent traditional drug promotion and distribution channels by implementing new methods of marketing: Terramycin was not only being sold directly to hospitals and retailers, Pfizer's small team of sales reps would target a small region and meet directly with every accessible healthcare professional in the region to promote their drug. The sales reps would then leave generous samples at every visit. Pfizer also sponsored golf tournament, ran noisy hospitality suites at conventions and ran multipage advertising in medical journals.

While detailing (sales rep visiting physicians) and pharmaceutical advertising in medical journals existed in the 1940s, Pfizer attained a degree of lavish promotion never met by competitors. Pfizer became the largest advertiser in the American Medical Association's journal. The Terramycin marketing campaign cost $7.5 million and, after 12 months, Terramycin's sales accounted for 25% of Pfizer's total sales (Derdak 2001, 359). Confronted to the success of Pfizer's promotion blitz, competitors had to follow and began to promote their products in the same way. Between 1950 and 1960, total drug promotion in the pharmaceutical industry rose from 3% to 7.4% of sales (Temin 1980, 84).

The New Face of Big Pharma

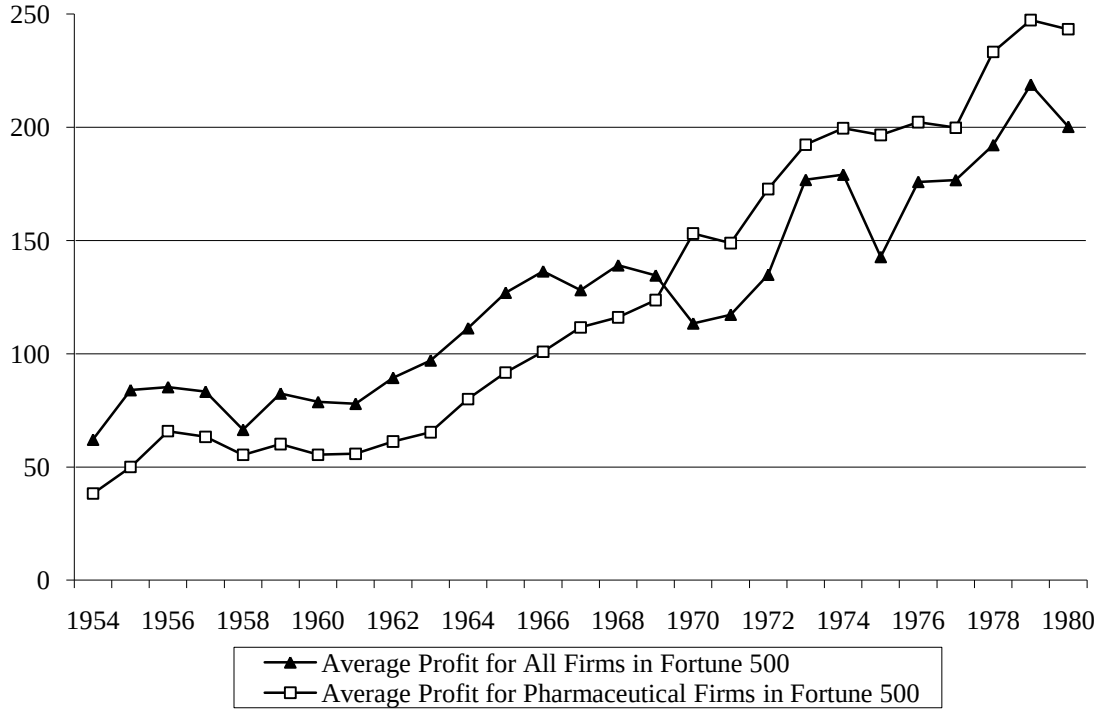
The road to success for core companies required both important R&D and marketing capabilities. U.S. pharmaceutical firms that developed only through the R&D or marketing

path had to acquire the missing capabilities through mergers and acquisitions. The R&D focused Merck merged with the marketing oriented Sharp & Dohme in 1953. Olin acquired the vertically integrated and R&D focused Squibb in 1953. Warner merged with Lambert Pharmacal in 1956, and Schering acquired White Laboratories in 1957. The consolidation movement continued until the 1970s; Warner-Lambert acquired Parke-Davis in 1970, Schering and Plough merged in 1971 and Smithkline & French acquired Beckman in 1976. Thanks to the 1938 Act, the crash war programs, the therapeutic revolution, the marketing revolution and the institutional structures providing great monopolistic capacities to core companies, many American firms were first movers in the emerging blockbuster model. Vertically integrated drug firms from production to distribution came to dominate the market, transforming the face of Big Pharma.

In terms of differential accumulation, the pattern for American Big Pharma consistently followed the same one as for the rest of the American industry until 1980, even getting ahead of the rest of the industry in 1970 (Figure 4.3). The pharmaceutical sector can already be considered a mature industrial sector with major dominant firms when the Fortune 500 began collecting data in 1954.

Figure 4.3: Big Pharma Differential Accumulation 1954-1980

Profits of an average U.S. dominant pharmaceutical firm as compared to an average Fortune 500 firm (in millions of constant 1984 US$)



Source: Fortune

The transformation of Big Pharma is first and foremost the emergence of dominant American integrated pharmaceutical firms working under the blockbuster model. Nevertheless, some foreign competitors in the global arena also managed to become first movers in the new business model, but others were simply missing the boat. While the two revolutions shifted dominance from Germany to the U.S., some pharmaceutical firms in England, France, Germany and Switzerland nonetheless managed to jump onboard of the blockbuster model bandwagon.

In England, the three important players in pharmaceuticals after World War II were Glaxo (now part of GlaxoSmithKline), Beecham (now also part of GlaxoSmithKline) and ICI (which pharmaceutical division later became part of Astra-Zeneca). Glaxo, established in 1873 under the name Nathan and Company, was designated by the British Government as the leader of its wartime penicillin program, which allowed Glaxo to develop important R&D capabilities and diversify its production. Beecham, established in 1859, was Britain's largest OTC producer and opened its first research unit only in 1947. It introduced second-generation penicillin in 1957 and started to focus on ethical drugs, while it developed its marketing capabilities through acquisitions (Chandler 2005, 249-51). As for ICI, the English cartel in dyestuff chemicals formed in 1926, it met wartime needs with its pharmaceutical research and manufacturing facilities during World War II by producing penicillin, sulfa drugs and treatments for malaria. In 1954, ICI's pharmaceutical division became independent and focused on ethical drugs while benefiting from ICI's distribution network.

In France, Rhône-Poulenc (now part of Sanofi-Aventis), is an example of a company that missed the opportunities of the therapeutic revolution. Because of the German occupation during World War II, Rhône-Poulenc missed the cascade of discoveries that transformed American and British companies (Chandler 2005, 255-6). Rhône-Poulenc, with few innovations, remained a small player in Big Pharma's global arena until massive government interventions in 1990 made the French company a significant competitor.

In Germany, the situation was very different. I.G. Farben's domination in chemicals came to an end with the end of the Second World War, and its directors were tried in Nuremberg for war crimes. In spite of extensive incriminating evidence against the board of directors, they received light sentences, none of which was longer than four years. Journalists

covering the proceedings at the time indicated that the light sentences could be explained by the judges' unwillingness to expand their definition of war criminals to businessmen (Derdak 1996, 76). The I.G. Farben plants were operated under Allied supervision from 1947 until it was dismantled in 1952. All patents were taken away as war retribution. Bayer and Hoechst became independent corporate entities. Bayer was an important player in the therapeutic revolution since it introduced the screening method in 1935, which led to the discovery of *Prontosil*, a sulfa drug that could treat syphilis (Pignarre 2003, 41). Bayer and Hoechst, however, benefitted little from the therapeutic revolution of the time due to Allied supervision. Independent in 1952, Bayer quickly recovered, by rebuilding its capabilities mostly through acquisitions, and expansion overseas. Hoechst achieved the same result through internal investments (Chandler 2005, 238). In 1956, Hoechst even discovered the first oral anti-diabetic: Tolbutamide. Bayer and Hoechst nevertheless remained conglomerate style chemical companies producing drugs almost as a sideline.

In Switzerland, the cartel Basel AG remained alive and well after the war. Under the American antitrust law, however, the Basel AG cartel was not allowed to trade anymore with the United States. Unwilling to abandon its lucrative U.S. subsidiaries, Basel AG dissolved in 1951 into its original components: Ciba, Geigy and Sandoz. Ciba and Geigy were especially successful in the therapeutic revolution, even without the help of a U.S. crash program in antibiotics. They introduced the first important non-steroidal anti-inflammatory drugs, phenylbutazone, an important diuretic, hydrochlorothiazide, and an antidepressant, imipramine. Ciba merged with Geigy in 1970, and then with Sandoz in 1996 to form Novartis.

Another important Swiss pharmaceutical company that was an active player in the therapeutic revolution was Roche, established by the Hoffman family in Basel in 1896. Due to the small Swiss market, Roche had developed an international marketing organization to produce and distribute its products abroad. Between the two wars, Roche developed techniques for large-scale production of vitamins, capturing up to 70% of the world market in vitamins by 1971 (Derdak 2003, 191). Its capabilities in R&D made Roche a very important player of the therapeutic revolution with the discovery of an anti-tuberculosis drug and the introduction of tranquilizers like Librium and Valium.

By the beginning of the 1960s, the modern GPB was constituted. Mature core companies, American and European, dominated and organized the global pharmaceutical "market", with most firms based in the United States. Not all Big Pharma firms were yet transnational corporations, but the globalization process was about to intensify. Competition was generated through the discovery of patentable drugs by corporate entities vertically integrated in order to market their own products. R&D and promotional expenditures rose sharply, since they were the main weapons for success in the GPB. Still, regulatory transformations were about to implement another major change to the emerging business model in the 1960s and 1970s: the emergence of Randomized Clinical Trials (RCTs). RCTs changed the character of the therapeutic and marketing revolutions by making the process of development more rigorous, and more costly. While the therapeutic revolution began to fade away, RCTs began reorganizing the whole industrial dimension of the knowledge structure in pharmaceuticals.

The Regulatory Revolution and the Emergence of RCTs

Before the 1960s, the process of pharmaceutical discovery was characterized by lax regulations, and was sometimes conducive to dangerous "accidents". For example, chlorpromazine, discovered by Rhône-Poulenc in 1949, was administered to schizophrenia patients within months after having first been synthesized. Imipramine was discovered by Geigy in 1957, and only few weeks elapsed between its synthesis and first administration to patients, without any toxicity test, clinical trials or study of its pharmacological action on the body (Le Fanu 1999, 246-247). The least that can be said is that the existing protocols were not very demanding. Those are huge contrasts with today's RCTs, with which it takes around twelve years between the discovery of a new drug and its commercialization.

The turning point that forced the tightening of safety regulations was the thalidomide scandal. Thalidomide, a sleeping pill introduced first in 1957, was prescribed to pregnant women before any toxicity tests were done. The drug was off the market in 1962 after the discovery that thalidomide caused important fetal malformations. It is estimated that 12,000 children were born with malformations, and the images of babies with missing limbs became, in public opinion, the symbol of negligence and avarice of the pharmaceutical business. In the United States, regulatory controls were already tighter than in the rest of the world and, while thalidomide was available in most developed countries, it had not yet been approved in the American market, in spite of pressures made on regulatory authorities[59]. The global public outcry, as well as the idea that a conscientious bureaucrat regulating the American

[59] In the case of thalidomide, it was one FDA reviewer, Frances Kelsey, who refused the approval of the drug in spite of important pressures by the manufacturer. In 1962, in recognition of Kelsey's vigilance, President John F. Kennedy presented her with the medal for Distinguished Federal Civilian Service, which is the highest honour that can be bestowed upon a U.S. civilian (Bren 2001).

drug industry spared thousands in the United States, set in motion a global momentum for new regulations requiring stricter testing of new drugs. The FDA became the model for national regulatory agencies (Redwood 1987, 9), and American regulations began to set the pace for global regulations.

Pressure for stricter regulations existed before thalidomide, but the scandal opened wide the door to reforms. In 1962, the powers of the FDA were widened by the Kefauver-Harris Act, calling for more transparent advertising and labeling for drugs, but also requiring drug manufacturers to provide proof of the safety and efficacy of new drugs. While the FDA was now indirectly setting standards on a global scale, the "proof-of-efficacy" requirement transformed the workings of pharmaceutical innovation by the implementation of RCTs. Pharmaceutical discovery, until then led by chemists blindly synthesizing molecules to be tested openly on patients, was about to be transformed into the more "elegant" and scientific process of RCTs. The stages of RCTs were presented in Chapter 3, where their length and onerous costs were emphasized. RCTs existed before 1962 but they developed slowly in the 1960s and 1970s with mounting pressures from regulatory agencies, and gradually became the core of the discovery process. Additional regulations were also put in place in the U.S. after 1962 (table 4.2).

Table 4.2: The U.S. Regulatory Revolution in Pharmaceuticals

Year	Regulations
1963	Regulations issued for good manufacturing practices
1966	Preclinical guidelines issued for reproductive, teratology, perinatal and postnatal studies
1968	Preclinical guidelines issued for toxicity testing
1970	Regulations specifying requirements for "well-controlled investigations" to produce "substantial evidence" of efficacy
1970	30 day delay for initiation of testing in humans after submission of Investigational New Drug (IND) application.
1972	Preclinical guidelines issued for chemistry, expanding requirements for drug manufacture, and quality control
1977	Clinical guidelines issued for various drug classes
1978	Regulations specifying good laboratory practices (standards for test protocols, quality control, recordkeeping, equipment, facilities, etc.)

Source: Pharmaceutical Panel (1983, 61-62).

Tighter regulations means higher production costs for pharmaceutical firms. While Big Pharma was reticent, at first, to be subjected to new regulations, it quickly saw in them an opportunity to increase its monopolistic power: "This increase in costs was thus an instrument of power. The more demanding were the regulatory authorities, the more concentrated became capital, and more competitors were thus eliminated" (Pignarre 2003, 75, author's translation). What was at first an obstacle for business as usual became an intangible asset for dominant pharmaceutical firms, increasing differential accumulation between Big Pharma and smaller firms. The burdensome and onerous machinery of RCTs thus developed with the consent of dominant firms. For example, an economist from the libertarian CATO institute, Michael Cannon, explains that big drug firms quietly acquiesce to

this burdensome red tape because it acts as a barrier to entry against newcomers that do not have the cash or lobbying power to navigate the FDA (Economist 2007).

RCTs are not only costly, they demand a large network of connections with doctors and professionals that agree to perform the clinical trials. The control over such networks is also an important barrier to entry. For example, Philippe Pignarre, who worked in the small-size Laboratoires Delagrange before it was acquired by Synthelabo (now part of Sanofi-Aventis), related a revealing episode about sulpirides in a personal communication (e-mail on July 4, 2007). In the mid-1970s, the small-size Laboratoires Delagrange wanted to study its first neuroleptic drug (sulpiride). Larger firms, such as Rhône-Poulenc or Janssen, considered that their markets for chlorpromazine or haloperidol were being challenged and did all they could to block Delagrange, by making sure that all renowned medical investigators would refuse to work with them. In the end, sulpiride managed to get through the RCTs, but it took Delagrange much more effort and money than anticipated. This episode almost ruined the possibility to discover the whole branch of substitute benzamides, which are still used today in the treatment of schizophrenia.

In the U.S., regulations remained more stringent than elsewhere due to the requirement for a longer length of RCTs and the approval process also took longer than in Europe. This created a "drug-lag", which meant that new drugs reached patients in America later than in most other countries. The drug-lag acted as a non-tariff barrier, delaying competition from new drugs, but it also served as encouragement for American firms to globalize their facilities (Redwood 1987, 9):

> The effect [of the drug lag] was to strengthen American firms through the 1960s and 1970s because their dominant hold on their home market was hardly challenged, while at the same time they were provoked gradually to shift the emphasis of their innovative efforts away from the USA with long-term benefits to their multinational stance. The loss was America's rather than that of American firms.

In order to better recover the cost of R&D as fast as possible, the drug lag forced American firms to intensify their multinationalization. The creation of American subsidiaries in other major markets with shorter regulatory periods, allowed American firms to deploy marketing machines in the world's major national markets. Conversely, at the beginning of the 1980s, the foreign penetration of the American market remained the lowest after ultra-protectionist Japan. Contrary to Japan, however, American firms did not confine themselves to their national market. While table 4.3 shows that 53% of corporate sales by American pharmaceutical firms were made in their home market, one must keep in mind that the American market was also the largest on the planet. American firms had in fact captured half of all multinational sales, which are sales made through foreign subsidiaries (Redwood 1987, 294).

Table 4.3: Foreign Penetration of National Pharmaceutical Market in Developed Countries and Home Market Dependence of National Firms

Market	Home market % of world market (average 1980-1983)	Foreign penetration (% of market held by foreign firms in 1983)	Home dependence of national firms (% of corporate sales in home market, average 1980-1983)
U.S.	24.3	20	53
Germany	7.8	45	37
France	7.5	45	61
U.K	5.0	68	24
Switzerland	0.7	58	5.5
Japan	18.1	16	98

Source: Redwood (1987, 288-298).

It is true that the implementation of stricter regulations sometimes occasioned some clashes between the FDA and certain firms, but, overall, dominant core companies did not fiercely oppose the new regulatory regime. The implementation of modern RCTs, which served so well the interests of dominant American Big Pharma, had two direct consequences: 1) increased investments in R&D and 2) a slow-down in pharmaceutical innovation. Between 1964 and 1980, American R&D expenditures in pharmaceuticals rose from $278 million to $2,430 million, and world R&D expenditures in pharmaceuticals rose from $500 million to $7,200 million. The average real annual growth in world R&D expenditures in pharmaceuticals was on average 10.2% per annum between 1964 and 1981 (Redwood 1987, 173). In contrast, the global introduction of new chemical entities went from 431 between 1960 and 1965, to 277 between 1975 and 1980 (Reis-Arndt 1987).

Note that the close correlation between the rise in RCTs and the decline of innovation should not be interpreted as direct causality by insisting that "over-regulation" is the primary

cause of the decline in innovation (see for example Epstein 2006). While the implementation of RCTs did increase the costs of discovery, an additional but equally important explanation must also be considered to account for the dearth of new drugs. According to Le Fanu (1999, 248), the therapeutic revolution occurred by synthesizing compounds, without the basic understanding of disease processes. The new drugs were discovered through a process of trial and errors by testing all available compounds to all existing conditions. Focusing only on the *screening* method to synthesize new compounds can only exhaust, sooner or later, the possibilities of always finding new chemicals to test this way. The therapeutic revolution was, in large part, the result of finding the low hanging fruits that could be obtained through the *screening* method. RCTs participated in the faltering of the therapeutic revolution by increasing the cost of discovery, but it was not the only factor.

The regulatory revolution also transformed the medical practice in ways that remain with us today. The definition of "effective treatment" of disease is now understood through the criteria for chemical compounds to meet approval by regulatory authorities ─ that is, the criteria for a successful RCT. Any alternative treatment that cannot be proven through RCTs becomes invalid in the eyes of doctors: "Clinical trials defined the alpha and omega of what is a medicine. *They have not only been a device to control safety: They quickly transformed into a tool for regulation and became the core of the process of invention itself*" (Pignarre 2003, 52, author's translation, italics original).

For instance, Pignarre (2001) shows how psychiatry was radically transformed by RCTs by explaining how depression became an epidemic. The first antidepressants and chlorpromazine, which treats schizophrenia, were discovered before the implementation of RCTs, at a time when there were different medical theories about the human psyche. With

RCTs, popular medical theories like psychoanalysis or concepts like neurosis became simply medically irrelevant since treatments now had to have proven efficacy through RCTs. To treat depression, RCTs provide a proof of efficacy that is independent of the subjective experience of each patient, meaning that their mental condition has to be treated without regards to their past life experiences. Everything has to be quantified and compared from one patient to another, which invalidates any understanding of depression in subjective terms. But a question remains: What is depression? RCTs are based on the use of chemical compounds and the analysis of their efficacy to treat a condition; to put it bluntly: one injects a virus in a rat and uses a chemical compound to see if it kills the virus. Depression, however, is not something that can be injected in rats, and drug compounds can only act on symptoms of depression, not on its causes. What then is depression? In the psychiatric practice it became any symptom that can be cured by the antidepressant. If Prozac can reduce sadness, shyness or the pre-menstrual syndrome (PMS), then sadness, shyness or PMS can be considered as forms of depression. Specifically, to the question about how depression became an epidemic in modern day society, Pignarre answers that it has less to do with people being more stressed than before, or with medical practice that can now better detect depressed patients; it is, instead, because of the huge power of pharmaceutical firms to redefine depression through new antidepressants that are marketed after successful RCTs (Pignarre 2001, 105, author's translation):

> Depression is a market for the pharmaceutical industry, and a market never exists by itself, waiting for products to fill it. A market evolves; it is constructed, formatted, extended or restrained simultaneously with the invention of products, which are the basis of its configuration [...] The pharmaceutical industry explores and develops the area of depression by putting in place a machinery, a series of effective arrangements, which integrate doctors,

> patients and drugs into a unique social fabric. [...] What can we do in a hazy world where the criteria for truth are being fabricated at the same time as the objects that have to be judged?

The power of RCTs is not only to prove the efficacy of compounds, it is also to socially differentiate between the normal and the pathological and to medically dictate how the pathology must be treated. RCTs are at the heart of structural competition in pharmaceuticals; that is, a competition based of the reshaping of the knowledge structure. RCTs allow to determine the precise efficacy of a drug and thus to determine on what terms it has to be prescribed. According to the results of RCTs, "niches" are discovered for the product, and this discovery usually redefines or re-creates the medical markets by redefining pathologies. From there, the medical community is brought to examine the niche and the medication for the niche more thoroughly in a way that expands or restrains the medical market for the drug. This process of examination entails companies intensively promoting their products to doctors and lobbying medical organizations to obtain the most favorable opinions.

It would be wrong, however, to consider this process in terms of Manichean manipulations; researchers do not normally endorse ideas they do not believe in, medical studies usually are of great quality, and are published in peer-reviewed journals. There is no need to manipulate researchers and doctors in order to redefine pathologies and markets according to the interests of pharmaceutical firms. The latter simply have to provide adequate funding for well-defined programs. Minor strains of thought suddenly receive important funding for research; marginal research teams are being considered for important financial grants for studies they could not fund before; grants and prizes are offered for studies

concerning the new niche; conventions and conferences are organized around the new pathology; phase IV clinical trials inculcate new prescribing habits in doctors; CME teaches doctors the pathology and its treatment; brochures are being sent everywhere; samples are left in doctors' offices; and sometimes direct-to-consumer advertising is also used to inform the population about the new "condition" that exists and the treatment that is available. Along the way, the medical knowledge structure has been transformed, a host of new drugs are being sold and everybody believes they have participated in real medical progress.

In such a context, denouncing corporate manipulations is, most of the time, futile. Everything is normally done in good faith by every actor. However, in this environment, it should not be surprising that prescribing habits of doctors can deviate from their scientific basis. For example, scientific studies show that, in France, between 40% and 95% of the prescriptions for statins, hypolipidemic agents, are baseless (CNAM 2003). Sometimes, an entirely new generation of a drug can prove less effective than the preceding generation, even if its cost is ten-fold that of the previous version (now without patent protection), like in the case of antipsychotics (Jones et al. 2006) or antihypertensive drugs (ALLHAT 2002).

RCTs are central in favoring a medicine based on remedies instead of prevention. Growing concerns can be raised in terms of overmedicalization (Abramson 2005; Moynihan and Cassels 2005), in terms of corporate influence of the medical profession (Angell 2004; Healy 2004; Kassirer 2005). But any depiction of the GPB in terms of powerful corporations deceptively manipulating the whole process, duping doctors, is pointless. Such power is impossible without the consent of those who participate. Pharmaceutical firms are not solely responsible of the actual RCTs system, they are simply part of it, even if they certainly have vested interests in the knowledge structure, and definitely use all their capacities to influence

the process of discovery and the reshaping of the medical knowledge structure according to their interests. RCTs are the "name of the game" for pharmaceuticals, since they are central to shaping medical knowledge and developing drug consumption habits. Due to their prohibitive cost, RCTs are often the kept territory of dominant pharmaceutical firms. As such, Big Pharma controls and constantly reshapes the knowledge structure in pharmaceuticals by integrating all players into a huge process that renders the legitimate criteria for medical truth and good health ─ a process through which only dominant pharmaceutical firms have enough organizational capabilities to maneuver. Here, control over this process is a central intangible asset for Big Pharma.

The regulatory revolution did not change the face of Big Pharma; it transformed the institutional structure in which Big Pharma evolved by consolidating the power of its members. It implemented new barriers to entry and offered Big Pharma more room to deploy its capabilities to re-shape the knowledge structure. In spite of the decline in innovation, profitability increased for Big Pharma, allowing positive differential accumulation against the rest of the sector, as well as other sectors. Big Pharma, however, was not immune to new challenges, as the subsequent section makes clear.

4.4 Big Pharma's Big Scare

The implementation of RCTs had become an important source of power for Big Pharma. Combined with the blockbuster business model, emerging from the therapeutic and marketing revolutions, it explains, in part, why the dominant American pharmaceutical firms

got ahead dominant firms in other industries in terms of differential accumulation. The setting, however, was far from perfect for American pharmaceutical firms in the 1970s, since it was also a period which witnessed a revival in generics, threatening important market shares for Big Pharma. Furthermore, globalization produced new challenges for Big Pharma; namely, the emergence of generic competitors in developing countries and adverse national policies aimed at disciplining dominant pharmaceutical firms in foreign markets. For American firms, those trends were perceived as threats to their long-term dominance in the sector. These threats shook dominant players by the end of the 1970s, and Big Pharma began to call on the help of the state.

Revival of Generics

As mentioned above, the therapeutic revolution occasioned a drop in generic prescriptions from 40% in 1948 to 5% in 1965 (Redwood 1987, 11). While new brand-name products arrived regularly on the pharmacist's shelves, doctors were somewhat beguiled by the lure of therapeutic innovation in its new clothes of promotion: salesmen meeting with them personally, treating them with great respect to explain in detail the new medical wonders on the market and leaving them with abundant samples. Brand promotion and "quality assurance" over generics developed brand loyalty among doctors. As if this intensive marketing was not enough for generics producers to contend with, a scandal involving unscrupulous generic drug manufacturers that sold counterfeit drugs brought the authorities to implement anti-substitution laws in all American states. The anti-substitution laws required pharmacists not to substitute prescriptions for brand-name products with generics, unless authorized by doctors (Suh 1999, 260). Patent holders were thus able to wipe

out their generic competitors. The high level of prices allowed brand-name manufacturers to finance important marketing campaigns, which further contributed to important goodwill for brand-name drugs. With increased brand-name loyalty, it became impossible for generic products to obtain any significant share of the retail prescription market (Steele 1962, 161). Some analysts even suggest that brand-name loyalty is more effective than patents to guarantee higher returns (Lall 1985, 230). In any case, without the possibility of generics, price elasticity became almost non-existent, allowing subsequent price increases, financing more vigorous selling campaigns. In 1967-1968, at the U.S. Senate Hearings before the Subcommittee on Monopoly on "Competitive Problems in the Drug Industry" (quoted in Redwood 1987, 231):

> the "absence of effective price competition in the sale of many products" was put forward as the root cause of high drug profits. It was suggested that barriers to entry arising from advertising and brand promotion were "the single most important explanation for differences in profit rates in American industry". The sheltering from price competition of patented and brand-promoted drugs, it was declared, had brought about a situation in which "generics often have difficulty selling at all."

Importantly, in the 1970s, many of the patents protecting the fruits of the therapeutic revolution expired. The growing marketing of expensive, but unimportant, brand-name me-too drugs in the 1960s and 1970s, and pressures for cost-containment in the American health system, brought about major arguments for reintroducing generics as a driving force to lower drug prices. Anti-substitution laws were repealed gradually in the 1970s rendering the demand for drugs more elastic, and creating a "revival" in generics (Redwood 1987, 230-249). Generics, as a share of all prescriptions in the United States, went from 5% in 1965 to 9% in 1974 and 15% in 1983 (Redwood 1987, 239). After the implementation of the Hatch-

Waxman Act in 1984, which alleviated the regulatory burden for generic producers to market their products, the share of generics continued to grow in the U.S. to 29% in 1988 (Ballance et al. 1992, 46), and to 50% in 2005 (PICTF 2006, 36). Those numbers, however, have to be put in perspective in terms of value, since generics are cheaper than brand-name products. In 1983, 15% of generics as a share of all prescriptions in absolute terms meant only a 5-6% of the share of all prescriptions in value (Redwood 1987, 245). The proportion jumped to 11% in 2004 (PICTF 2006, 36). Those smaller proportions nevertheless meant that even while generic penetration may be limited, significant market shares can be lost for brand-name products.

Globalization

The process of globalization in the GPB has been an opportunity for pharmaceutical firms. However, to shift from the national arena to the global arena is always a risky endeavor, since firms are confronted by different national policies, local institutions and culture, and foreign competitors. Globalization is a process in which firms can either lose or gain important power. While some inter-penetration of major drug markets existed during all of the twentieth century, the new business model that arose with the therapeutic and marketing revolutions brought a real globalization pattern where Big Pharma firms began to enter as many national markets as possible.

In order to quickly recover their R&D costs, integrated pharmaceutical firms developed important marketing capabilities in major drug markets. Marketing activity has a provincial nature; it needs to adapt to local disease patterns and to the national tastes and preferences of doctors and patients. National regulations have also been an important factor in favoring

foreign investments by pharmaceutical firms (Ballance et al. 1992, 69): registration of a drug sometimes requires that trials are undertaken locally; policies governing prices and methods of reimbursement often favor local production over imports; and import controls can encourage firms to "move behind" trade barriers by setting up local production facilities. Governments in major drug markets, like Spain or France, and most developing countries prohibited the import of most finished medications, encouraging multinationals to set up local subsidiaries. Other governments sometimes offered bargains to foreign firms establishing local R&D facilities: price or reimbursement concessions, tax benefits or capital grants (Redwood 1987, 88). It is interesting to note that, in the case of pharmaceuticals, it was those types of protectionist policies that, in the end, accelerated the pace towards multinationalization. Globalization was a natural route for Big Pharma: after capturing their national markets, pharmaceutical firms tried to extend their reach by capturing foreign market shares (Ballance et al. 1992, 69): "The pharmaceutical industry consists of a large number of heterogeneous submarkets where firm concentration tends to be high. Such a market structure is conducive to internationalization as national oligopolies with stable domestic markets look elsewhere in order to expand sales". For all those reasons, Big Pharma came to favor foreign direct investment (FDI) instead of exports or licenses. By 1980, 26% of world sales in pharmaceuticals were locally produced in national markets by foreign-owned companies' subsidiaries, and only 13% of sales were achieved through the importation of foreign-made products (Ballance et al. 1992, 68-69). Multinationalization thus became more important in pharmaceutical world trade than exports.

The globalization process for Big Pharma, however, was not achieved at the same pace for all firms. German pharmaceutical firms began to globalize in the nineteenth century.

Their progress was halted twice as German subsidiaries and patents were seized by local authorities during the two World Wars. Due to their small home market, Swiss pharmaceutical firms globalized rapidly during the therapeutic revolution, setting forth a model for other firms: vertical integration with strong R&D, combined with global marketing capabilities. Post WWII American firms promptly followed the globalization path. As the oligopolistic leaders in the single most important national drug market, they began to globalize mostly in the late 1950s to market their drugs worldwide, and they were pushed to globalize further in the 1960s by the "drug-lag" specific to American RCTs (United Nations Centre on Transnational Corporations 1979, 9):

> United States TNCs have begun to depend increasingly on foreign markets for their R and D and sales. As the process of drug development in the United States has grown more costly and the gestation time for new products has lengthened, the United States firms have moved a large part of their clinical testing function overseas. This has resulted in a pattern whereby new drugs are first introduced abroad, with introduction into the United States market delayed until the FDA requirements are fulfilled. The size and importance of foreign markets as a sales outlet and contributor to the corporations' profits is also increasing for the United States companies.

The globalizing trend of American firms is illustrated by the quantity of manufacturing subsidiaries established by the 25 largest American pharmaceutical firms in the 1950s and 1960s as compared to before 1950: 15 were established before 1950, while 134 were established in the 1950s and 170 in the 1960s (Table 4.4).

Table 4.4: Establishment of First Manufacturing Subsidiaries Set Up by the 25 Largest US Pharmaceutical Firms until 1970

Area	Before 1950	1950-1959	1960-1970	Total
Western Europe	7	41	64	112
Latin America	6	65	55	126
Africa	2	7	13	22
Asia/Middle-East	0	21	38	59
Total	**15**	**134**	**170**	**319**

Source: Gereffi 1983.

French and British firms confined their activities mostly to the franc zone and the sterling area, respectively, leaving wide open the opportunity for Swiss and American firms to develop their facilities and capabilities worldwide. For example, American and Swiss companies captured important segments of national market shares held by foreign companies in different countries (Table 4.5).

Nevertheless, British and French pharmaceutical firms chose to follow their American and Swiss counterparts in the globalization process later in the 1970s. European pharmaceutical firms, in general, began moving behind the non-tariff barrier of the American "drug-lag", establishing a broad multinational base in the U.S., in order to directly market European drugs in the United States. The market share for U.S.-owned companies began to fall in different national drug markets, including the United States (Table 4.6).

Table 4.5: Market Share Held by Foreign Companies in Various Countries, 1973 (%)

Ownership	United States	Germany	UK	France	Canada	Brazil	Mexico
American	X	13	38	17	63	36	50
Swiss	13	9	11	9	11	10	9
German	1	X	7	5	2	13	7
British	2	2	X	4	5	2	4
French	0	2	5	X	2	3	4
Other	0	4	3	3	1	6	4
Total foreign ownership	16	30	64	38	84	70	78

Source: Pharmaceutical Panel, CTIETI (1983, 11)

Table 4.6: Market Share of US Dominant Pharmaceutical Firms
(U.S., U.K., Germany and Japan; Selected years)

Market	1965	1970	1975	1979
United States	86.9	83.5	80.8	79.8
United Kingdom	45.9	39.5	37.7	36.6
Germany	na	na	17.4	18
Japan	na	na	7	6.7
World	na	na	31.9	29.3

Source: Pharmaceutical Panel, CTIETI (1983, 40)

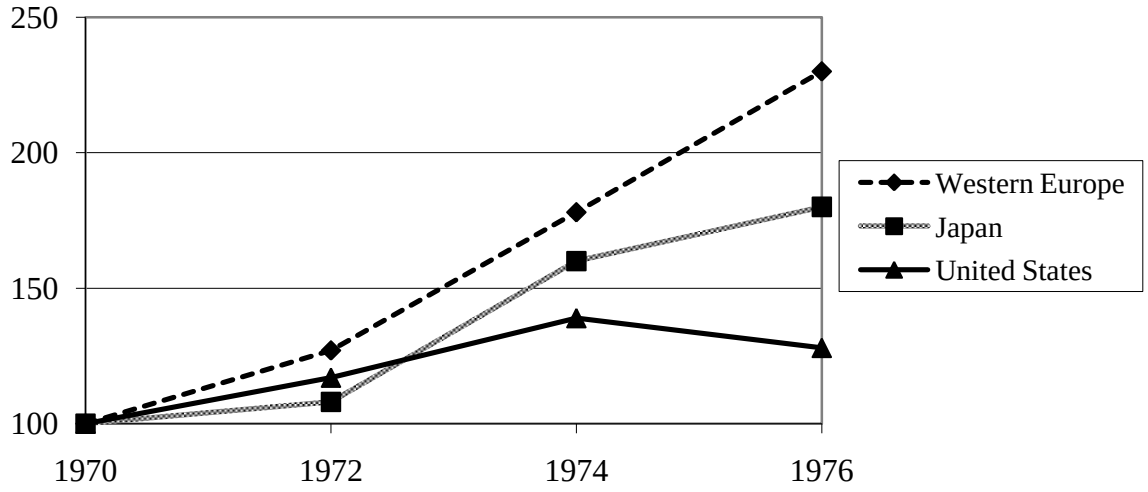
The "Yellow Peril"

Nonetheless, competition from European companies was not the only problem for American firms. The rise of the Japanese pharmaceutical business in the 1960s began to

gnaw away at American world market shares. In Japan, pharmaceutical firms did not benefit much from the therapeutic revolution, even if firms like Sankyo or Takeda, managed to manufacture some tranquilizers and antibiotics in the 1950s through licensing agreements with foreign firms. The Japanese drug industry developed rapidly in the 1960s with the implementation of the Japanese National Health Insurance System. This structure allowed almost full reimbursement for (mostly generic) prescription drugs and granted a profit to doctors for every drug prescribed, encouraging a generous volume of prescriptions. The Japanese pharmaceutical business experienced unprecedented financial success with an annual growth rate exceeding 20% (Derdak 1988, 704). The enactment of the 1976 patent protection laws also helped the transformation of the Japanese pharmaceutical business. In order to force its industry to be less reliant on foreign technologies, the government implemented stronger patent laws and increased prices for innovative products, making the national development of new drugs highly profitable. While many Japanese pharmaceutical firms became national giants thanks to a protectionist development model for the national industry, most of them remained confined to their national market. Between 1980 and 1983, 98% of the drugs produced by Japanese firms were sold in Japan (Redwood 1987, 131). The only firm that recently managed to establish a place for itself in the global arena is Takeda, by developing its own marketing capabilities abroad.

Compared to Japan and Europe, national pharmaceutical production in the United States in the 1970s showed a decline in the position of American companies (Figure 4.4). This relative decline for domestic firms was, in fact, emblematic of the general perception of the overall decline in the U.S. competitiveness, and it was taken very seriously by American businessmen who began to see Japan emerging as a peril.

Figure 4.4: Evolution of the Production in Europe, Japan and the U.S.
(1970-1976; 1970=100)



Source: Pharmaceutical Panel, CTIETI (1983, 60).

The Japanese breakthrough in pharmaceuticals, even if most confined to the national market, was understood as posing a threat to the development of American business. In order the assess the status of U.S. competitiveness in various industries, the National Research Council, along with the National Academy of Sciences, the National Academy of Engineering and the Institute of Medicine formed the Committee on Technology and International Economic Trade Issues (CTIETI). It analyzed, among others, the pharmaceutical industry, for which a Pharmaceutical Panel produced an important report in 1983. According to the report, Japan was considered as a clear and imminent danger to U.S. pharmaceutical firms. The Japanese success was the result of conscious policy decisions by

public authorities. Summarizing the Japanese breakthrough, the Pharmaceutical Panel (1983, 75) explained:

> Faced with overwhelming foreign competition in this market, the first step for development of a competitive domestic industry was promotion of generic-type firms. This promotion was achieved by denying (mostly foreign) innovators adequate patent protection, by disadvantaging foreign firms through non-tariff trade barriers, and by generous pricing policies. Once a production-oriented domestic industry was flourishing, however, the Japanese government, in the mid-1970s, began to systematically skew a broad mix of policies, especially patent and pricing policies, in favor of more innovative firms. This second stage of Japanese industrial policy contrasts sharply with recent U.S. actions, such as the eroding U.S. patent-life and pro-generic pricing policies for cost-control.

Because of its high-pricing policies and encouragement of prescribing by doctors, Japan even became the world's most important market with 26.9% of world drug consumption, followed by the United States (25.8%) and West Germany (10.1%). In terms of world market share for production, Japan ranked second with 23.9%, after the U.S. (24.9%) and ahead of West Germany (13%) (Industry Analysis Division 1984, 32). The numbers for Japanese growth were impressive, but Japan, which received massive foreign assistance from the United States after the Second World War, remained a contained threat to American firms. It was a market that developed for internal consumption, with firms confined to their market, and within which American firms were able to set up alliances to sell their products in Japan. The problem was the precedent Japan was setting for other emerging countries in Asia, which had the possibility to become more "aggressive" in international markets. As Drahos and Braithwaite (2002, 63) explain:

> Japan [...] performed the economic miracle, but this was with US assistance and for all its economic prowess Japan seemed, when it came to global politics, to have embarked on a strategy of retreatism or nonintervention. Japan did not try to set the rules of the game; it tried to beat the West under its own rules. There was no guarantee that the new "tigers" would be so politically compliant.

For American firms, the problem was simple: developing countries were finally developing, and it was bad for American business. Due to the differential nature of capital accumulation, growth in developing countries means a differential loss for developed countries. New economic competitors, following in Japan's footsteps, were about to emerge. South Korea, India and Brazil began to show the potential to compete. The "Asian tigers", or the "Gang of Four" (Hong Kong, Singapore, South Korea and Taiwan) were seen as a growing threat, as is shown simply by the discourse used to identify them in the West.

It came to be widely perceived that a "yellow peril" was emerging in the global business arena, including in pharmaceuticals. The South Korean pharmaceutical sector grew twelve fold between 1970 and the early 1980s. This growth was possible through the proliferation of copy drugs, which were unauthorized copies of brand-name products, and those copy drugs were taking substantial market share from the originators in the South Korean market (Redwood 1987, 283-285). India became the most advanced developing country in terms of pharmaceutical technology through a series of government interventions that restricted patent rights. Moreover, there was no patent protection for products in India, only for processes; and protection for processes was reduced in 1970 from 16 to 7 years, with provisions for compulsory licensing after 3 years, in exchange of a royalty fee that could not exceed 5% of the value of production (Redwood 1987, 278-283).

In the case of pharmaceuticals, as in other industries, emerging countries' success came to be perceived as a function of dishonest imitation of Western technology, based on patent systems that did not protect foreign technology. In the United States, the story was simple: American ideas and know-how were being stolen by developing countries, causing a decline in American competitiveness. Dominant American pharmaceutical companies fed the myth through important public campaigns which suggested that developing countries were stealing from the American mind. For instance, in an op-ed piece in the *New York Times*, Barry MacTaggart (1982), President of Pfizer International, accused the World Intellectual Property Organization (WIPO) of conferring international legitimacy on the theft of American technology by promoting technology transfer to developing countries. However, as Drahos and Braithwaite note (2002, 64):

> Perhaps what mattered about the story, though, was that it gave those in US policy circles a mission. The minority economies of the world like Singapore, Malaysia and Taiwan, which were not paying attention to US intellectual property rights, would be taught a lesson. [...] Absolutely crucial to the persuasive power of this story was economic analysis. The mode of analysis became the message. Economic reports turned the intellectual property story from one of moral transgression into the loss of markets and profits.

The American pharmaceutical business saw its world market share in the production of pharmaceuticals drop from 35.1% to 25.9% between 1970 and 1980, which caused a wind of panic among U.S. dominant pharmaceutical firms (Table 4.7).

Table 4.7:World Market Economy Share in Pharmaceutical Production
(by Location of Production; 1970 and 1980-1983; in %)

Country	1970	1980-1983
United States	35.1	25.9
Japan	12.4	17
West Germany	8.9	9
France	7.6	8.4
United Kingdom	5.6	6.3
Italy	4.7	5.2
Spain	2.8	2.6
India	1.5	2.5
Switzerland	1.9	2.1
Brazil	2.3	1.9
Canada	2	1.8
Argentina	1.6	1.5
Belgium	1	1.5
South Korea	0.1	1.5
Mexico	0.8	1.1
Others	10.4	11.7

Source: Redwood (1987, 114-116).

In the same way, the American world share in terms of R&D fell drastically in the same years. Foreign direct investments in pharmaceuticals and R&D facilities more and more favored foreign countries (Table 4.8).

Table 4.8: World Share in Pharmaceutical R&D expenditures
(by National Location, Selected Years, in%)

Country	1964	1973	1978
United States	60	34	28
West Germany	8	16	18
Switzerland	8	13	17
Japan	6	13	15
France	6	9	8
United Kingdom	6	6	8
Italy	3	4	4
Sweden	2	2	1
Netherlands	2	1	1

Source: Industry Analysis Division of U.S. Department of Commerce (1984, 37).

Among the reasons for this decline in the American world market share was the growth of pharmaceutical consumption outside the U.S. and the increasing number of countries, developing or developed, that *required* that a greater portion of the medicines for their national market be manufactured locally. It was such requirements that allowed the rise of competitors in Japan and in developing countries such as South Korea and India (Redwood 1987, 114-7). But it was this last point that was most annoying for American drug firms; the shift in national location in terms of R&D or manufacturing was not a problem as long as they remain in control of production, but it was another story to lose market shares as a company. Accordingly, the market shares of U.S.-owned multinational pharmaceutical firms declined in the same years, even if it was to a much lesser degree (see Table 4.6 above). From there it was easy for American pharmaceutical firms to link the decline of pharmaceutical production and R&D in the United States with the growing competition from

emerging countries "freeriding" on the American mind. From the perspective of American authorities, action was necessary to help their national firms compete with adversaries that were using "immoral" strategies.

Big Pharma in Decline?

The Pharmaceutical Panel of CTIETI (1983, 3, 76) summarized the decline of the U.S. pharmaceutical competitiveness:

- The U.S. share of world pharmaceutical R&D expenditures has fallen from greater than 60% during the 1950s to less than 30% in 1982.
- The number of new drugs entering U.S. clinical trials and owned by U.S. firms has steadily dropped from a yearly average of 60 in the mid-1960s to about 25 per year in 1982. In contrast, the number of foreign-owned drugs undergoing comparable trials has remained almost constant at about 20 per years.
- The percentage of world pharmaceutical production occurring in the United States has fallen from 50% in 1962 to 38% in 1968, to 27% in 1978.
- The share of pharmaceutical sales by U.S.-owned firms fell slightly in major markets during the 1960s and has been roughly constant since. In their domestic market, however, the share of U.S. firms was 87% in 1965 and 80% in 1982.
- During the 1970s, European pharmaceutical firms established a broad multinational base in the U.S. domestic market that was about to be used for direct marketing of European pharmaceutical innovation.
- The U.S. share of world pharmaceutical exports has fallen from greater than 30% before 1960 to less than 15% today.
- In 1982, Japanese firms accounted for over 16% of all U.S. patents issued for pharmaceutical and medicinal products. Japanese pharmaceutical houses are forming joint ventures with U.S. firms to market Japanese discoveries. These linkages are clearly first steps toward direct marketing of Japanese products overseas.

For the Pharmaceutical Panel of the CTIETI (1983, 70), the situation for pharmaceuticals was a function of a greater phenomenon:

> There are numerous similarities between the drop in pharmaceutical competitiveness and the general decline of the U.S. economy against Japan and Western Europe. Specifically, deterioration in U.S. shares of pharmaceutical exports, national ethical drug sales, and some aspects of pharmaceutical innovation such as patents are matched by comparable relative declines in many U.S. industries, including others in the high-technology sector. Adverse shifts in these specific features of competitive position are thus best explained by the more vibrant multi-industry growth of foreign economies and not by factors specific to the ethical drug industry.

The table was set for major reforms, and not only in pharmaceuticals. The received perception was that all high-technology sectors in the U.S. were under attack from foreign competition, and that intervention from authorities was necessary to preserve U.S. industrial leadership. What was at stake was nothing less than the American Way of Life (Pharmaceutical Panel CTIETI 1983, 77): "If the United States is to maintain standards of living comparable to those of other major industrial nations, it cannot suffer indefinite economy-wide declines in its share of world markets".

Ultimately, these perceptions of American decline, attributed to the "yellow peril", must be put in perspective. Drahos and Braithwaite (2002, 64) remind us that, in 1978, among the top twenty companies in the world, only one was Japanese (Toyota), and it was twentieth. In 1982, among the top twenty pharmaceutical firms in the world, 11 were American. Switzerland and Germany were next, each with three firms, while Japan had only one firm on the list (Table 4.9).

Table 4.9: Pharmaceutical Sales as Share of Total Sales of the World's Top Twenty Pharmaceutical Firms in 1982

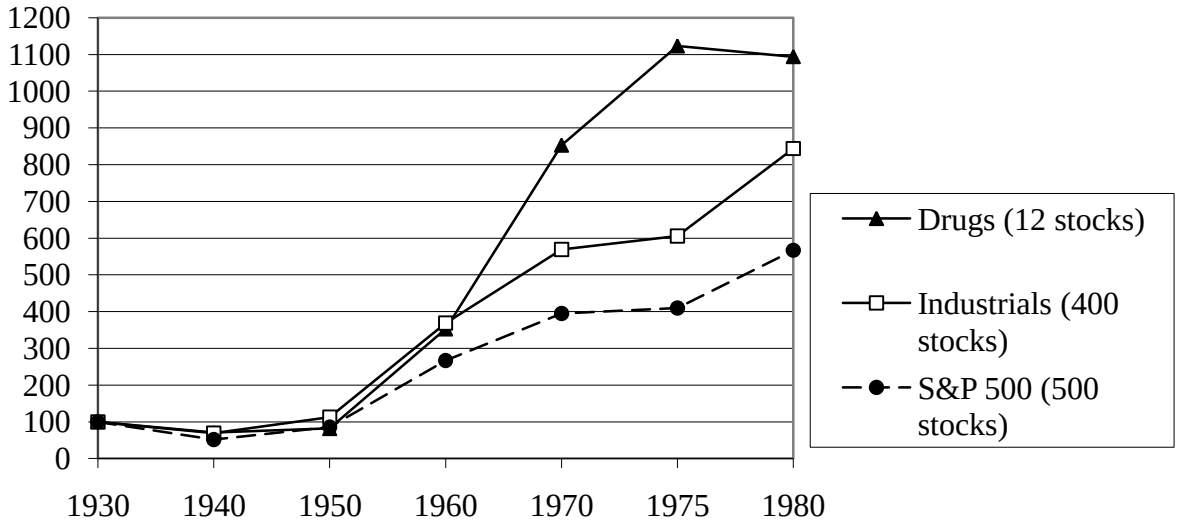
Firm	Country	Total Sales (Billion $)	Sales in Drugs (Billion $)	Drugs as % of Sales
Hoechst	West Germany	14.79	2.63	18
Bayer	West Germany	14.73	2.45	17
Merck	USA	3.06	2.21	72
AHP	USA	4.58	2.14	47
Ciba-Geigy	Switzerland	6.95	2.05	29
Pfizer	USA	3.45	1.7	49
Eli Lilly	USA	2.96	1.54	43
Roche	Switzerland	3.57	1.51	42
Sandoz	Switzerland	3.04	1.42	47
Bristol Myers	USA	3.6	1.36	38
SmithKline	USA	2.64	1.34	51
Abbott	USA	2.6	1.3	50
Warner-Lambert	USA	3.25	1.29	40
Takeda	Japan	2.18	1.29	59
Upjohn	USA	1.83	1.21	40
B. Ingelheim	West Germany	1.49	1.21	81
J&J	USA	5.76	1.12	19
Squibb	USA	1.66	1	60
Glaxo	UK	1.66	0.98	59
Rhône-Poulenc	France	5.55	0.9	16

Source: Industry Analysis Division of U.S. Department of Commerce (1984, 2).

American hegemony in pharmaceuticals might have been far from over, and the growing threat from Asia was surely overestimated, but such perceptions had a direct impact on the capitalization of U.S. dominant drug firms, and thus on their differential accumulation.

Figure 4.3 showed that differential accumulation for American Big Pharma was going rather well in the 1970s. However, this figure was based on realized earnings instead of anticipated ones. Since the perceptions were pessimistic for the U.S. pharmaceutical business, the market value for pharmaceutical firms was going down. Between 1975 and 1980, for the first time since the 1930s, there was a deaccumulation of capital for pharmaceutical firms as their expected earning-capacities decreased (figure 4.5).

Figure 4.5: Stock Price Appreciation on Wall Street 1930-1980
Drug Stocks, Industrials and S&P 500, 1930=100



Source: Standard & Poor, Redwood (1987, 222-224)

For pharmaceuticals, as for other high-technology businesses, the perceived threats of a "yellow peril" demanded a response by American authorities; important institutional changes were needed. What was to be done? The following years would witness the deployment of important U.S. strategies to preserve the dominance of U.S. firms in high technology

industries. The next two chapters show how the strategic institutional transformations favoring U.S. high-tech firms allowed the birth of the "New Economy", creating a boom in differential accumulation for pharmaceutical firms, and consolidating the power of American pharmaceutical firms in spite of continuously decreasing innovation.

5. DIFFERENTIAL BREADTH IN PHARMACEUTICALS: GROWING THROUGH MERGERS AND ACQUISITIONS

I saw come darting through a hedge,
Which fortified a rocky ledge,
A hydra's hundred heads; and in a trice
My blood was turning into ice.
But less the harm than terror,
The body came no nearer;
Nor could, unless it had been sunder'd,
To parts at least a hundred.
While musing deeply on this sight,
Another dragon came to light,
Whose single head avails
To lead a hundred tails:
And, seized with juster fright,
I saw him pass the hedge,
Head, body, tails, a wedge
Of living and resistless powers.
The other was your emperor's force; this ours.'

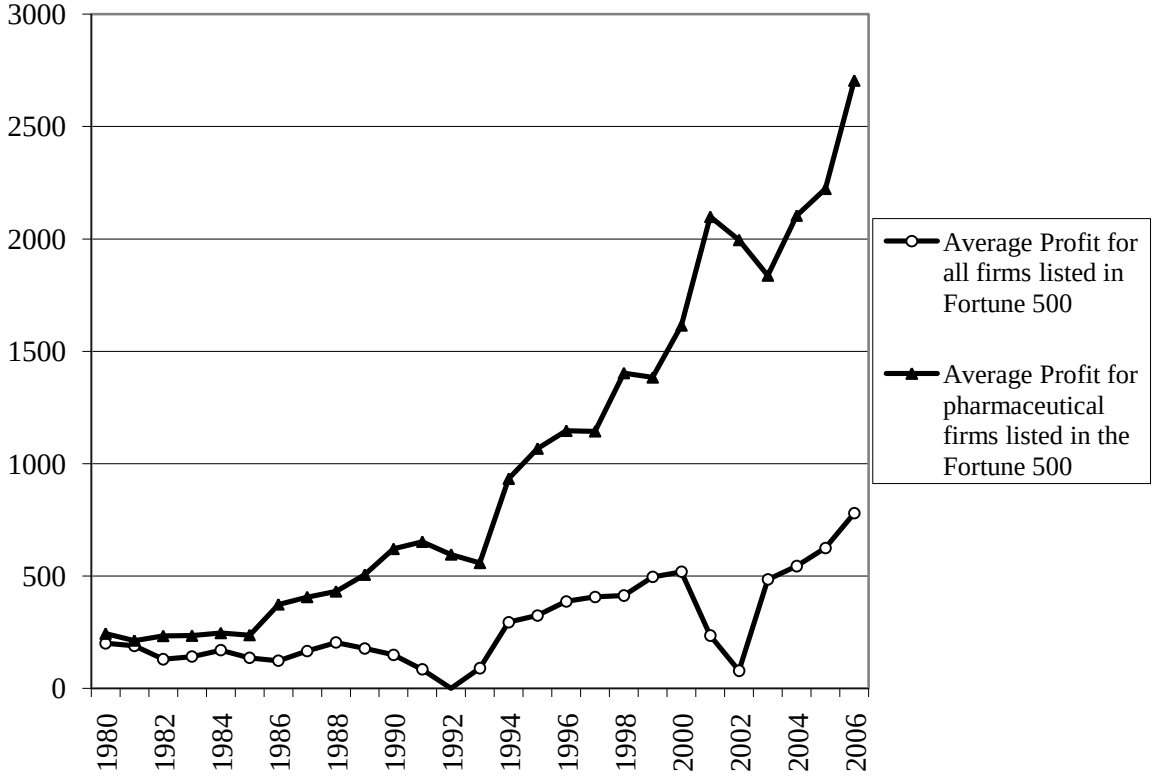
-Jean de la Fontaine, 1668
(The Dragon With Many Heads and The Dragon With Many Tails)

Beginning in the 1980s, there was a considerable paradigm shift in the United States, in order to restore American technological leadership on the globe. The perceived decline in U.S. competitiveness was to be actively tackled under the authority of the newly elected President Ronald Reagan. A series of policies were put in place by the American government, both nationally and internationally, to provide advantages (and differential earning-capacities) to American knowledge-based firms. This paradigm shift gave rise to what many called the "New Economy," based on the increased profits of American firms in high-tech sectors (Brender and Pisani 2004). Many authors provide differing explanations for this paradigm shift. For example, Coriat and Orsi (2002) suggest that a regime of innovation

was put in place, by extending intellectual property standards in the United States and by adapting the financial markets in order to favor venture capital. Drahos and Braithwaite (2002) argue, alternatively, that the relaxation of antitrust policies to allow mergers and the extension of global intellectual property standards were central to building American technological leadership based on monopolistic capacities. Krimsky (2004) emphasizes the multiplication of university-industry partnerships, while Loeppky (2005) and Castells (1988) suggest that state funding for technological innovation, like the public financing of the human genome project, were crucial to reinstating U.S. technological leadership. These accounts provide important knowledge of the paradigm shift at play since the beginning of the 1980s, but it is difficult to evaluate their respective influence, without any quantitative measure of the impact of the transformations they address. Understanding the importance of each element, however, is necessary in order to evaluate the nature of the accumulation regime that characterizes the pharmaceutical sector in the era of the "New Economy".

The analytical framework of differential accumulation provides a relevant proxy that allows one to quantify approximately the importance of the different factors at play. Using the historical data of American dominant firms' profits provided by the Fortune 500, and isolating the pharmaceutical sector from other sectors, the differential growth of profits for pharmaceutical firms provides a quantitative insight into the differential advantage of dominant "knowledge-based" firms in the pharmaceutical sector (Figure 5.1). Again, the explanation of the exact methodology can be found in Appendix A.

Figure 5.1: Big Pharma Differential Accumulation 1980-2006
Profits of an average U.S. dominant pharmaceutical firm as compared to an average Fortune 500 firm (in millions of constant 1984 $)



Source: Fortune

Figure 5.1 clearly shows a growing gap between pharmaceutical firms and the rest of the Fortune 500 since the middle of the 1980s. It must be considered that, for the pharmaceutical sector, this growing gap defines in quantitative terms what is usually called the "New Economy". The new accumulation regime at work for the knowledge-based firms can be observed in the pharmaceutical sector as the growing differential accumulation of profits. The reasons for this growing gap and the nature of this accumulation regime, however, are still to be explained. In logical terms, this growing differential accumulation of profits can be due to two trends:

1- The size of the pharmaceutical firms' assets is growing faster (or decreasing more slowly) than the average of Fortune 500 firms. In this case, following the concepts put forth by Nitzan (2001, 232), the term "differential breadth" will be used.

2- The rate of profit is growing faster (or decreasing more slowly) than the average of Fortune 500 firms. Following again the concepts put forth by Nitzan (2001, 232-233), the term "differential depth" will be used.

This chapter and the next one discuss in greater detail the evolving differential breadth and depth of the pharmaceutical sector, in order to better understand which elements are at the core of the growing differential accumulation. By analyzing the nature and content of this differential accumulation, it improves our understanding of the nature of the accumulation regime upon which the industry has been building since the mid 1980s, and which is usually associated with the emergence of a "knowledge-based economy". Chapters 6 and 7 will examine whether there is a growing differential depth in the pharmaceutical sector, as well as what the reasons for such growth might be. The present chapter examines whether there is a growing differential breadth in the pharmaceutical sector and, similarly, identifies reasons for such growth.

5.1 Differential Breadth in the Pharmaceutical Sector

Differential accumulation provides analytical tools to explore the causes for the growing profitability of the pharmaceutical sector in the 1980s. The first of these tools is the analysis

of the differential evolution of breadth. Breadth refers to the size of firms, and differential breadth relates to the differential growth of different firms. In order to measure differential breadth, it is first necessary to find a proxy to measure breadth (the size of firms). After identifying that proxy, the results of the evolution of differential breadth, obtained through different databases, will be presented and discussed.

Measuring Breadth

Different standards exist to measure the importance of firms: Revenues, equities, number of employees, assets or market value. Most of these standards, however, do not allow accurate measuring of firms' breadth. The FT500, the *Financial Times* listing of the most important firms, is based on market value. However, market value is wider than breadth per se, since variations in market value can be the result of differential depth (greater profit per unit), or even be caused by investors' hype alone. The Fortune 500 lists the most important firms according to revenues. This method of measuring the size of firms is problematic, since revenues include all gross incomes of a firm. The problem is that firms focusing on buying and selling, for example general retailers like Wal-Mart, can generate huge revenues, but with very little fixed capital, and with a very low rate of return on revenues. Equities, also cannot be considered a reliable standard, since they can vary not only according to the size of firms but also according to the financial structure of firms. For example, it was observed that many large growing firms in recent years bought back their equities in order to downsize the ownership of the firm and, in that way, generate higher returns for the remaining shareholders (Batsch, 2002).

Bichler and Nitzan (2002b, 52-53) favor measuring the size of firms by the number of their employees. Such a standard, however, implies that the size of firms depend on the number of paid labor hours, whereas some firms may require less human labor and more machines, which does not mean that they are necessarily smaller than firms that require more employees and fewer machines. In fact, Nitzan and Bichler use this standard to insist on the capacity for dominant groups, especially in the oil sector, to restrain general production by creating unemployment through stagflation. Nevertheless, employment and wages are measures of the overall earning-capacity or purchasing power distributed to workers as compared to firms. While this method is of interest in analyzing the struggle between labor and capital, it should not be considered an accurate measure of the firms' size.

The standard of overall investments is much more relevant to measure the size of firms. In modern accounting, investments are measured by the firms' assets financed by liabilities, owners' equity or by the reinvestment of the firm's profits. According to the International Accounting Standards Board (IASB 2001), "an asset is a resource controlled by the enterprise as a result of past events and from which future economic benefits are expected to flow to the enterprise". The firms' assets can be tangible (cash, property and equipment) or intangible. In modern accounting, the term "intangible assets" refers to patents, franchises, trademarks and goodwill. Veblen considered the latter to include any monopolistic capacity, while modern accounting measures it by the difference between book and market value when one firm acquires another. Note that investment in R&D, considered in American accounting to be expenditure rather than investment, does not translate automatically into firm assets, unlike investment in equipment. This way, only successful R&D that takes the form of

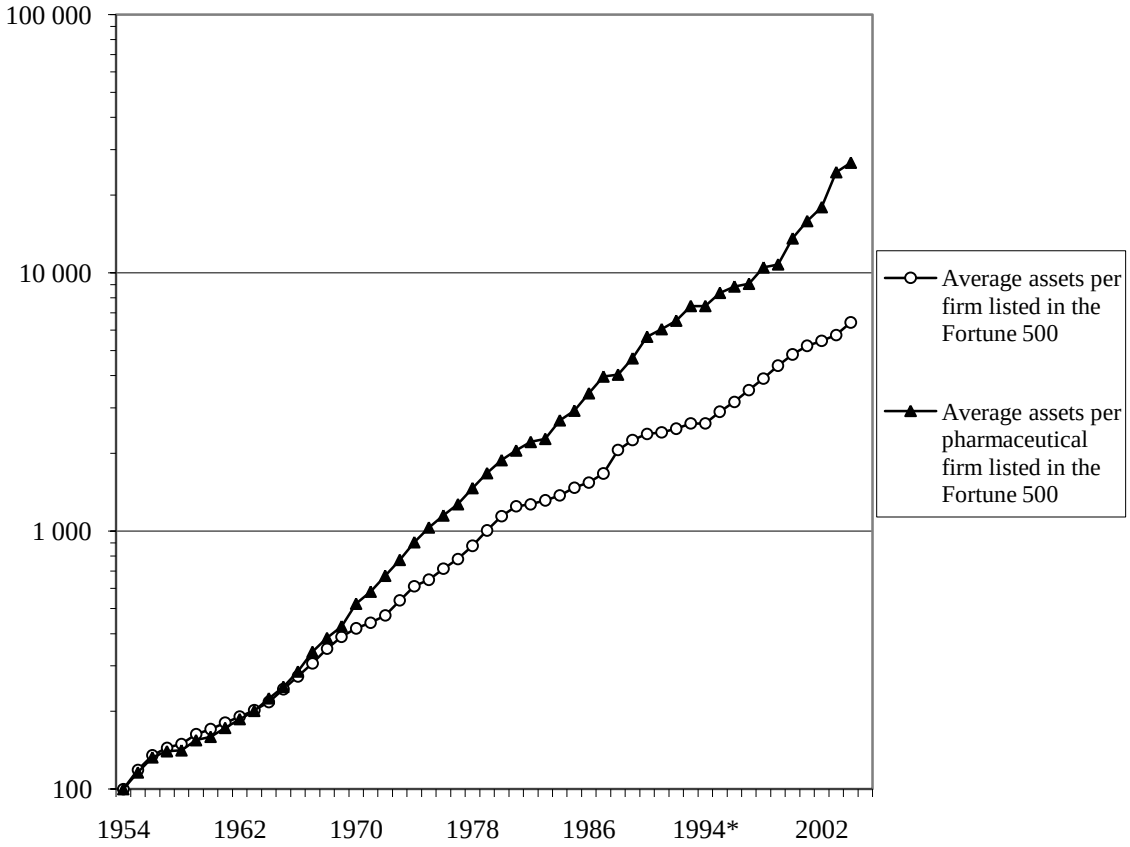
patents (appropriated knowledge) can become an intangible asset for the firm, but there is no direct value determination between the two.

The value of assets can be used as a proxy measure for the size of a firm. Assets can be measured by their market value (actual value on the market), book value (cost value when carried on the bookkeeping records of the firm) or replacement cost (cost to reproduce existing assets today). Since market value is determined by the earning-capacity of the asset, which includes depth, it should be discarded. The best measure for the value of the assets is without a doubt their replacement cost, the cost to build those assets today. The difficulty of obtaining such data, however, is extreme and the determination of the replacement cost of the assets for specific pharmaceutical firms would in the end prove impossible. The book value is an estimate of the firm's size and remains far from perfect. First, the value of an asset (for example, the land on which the plant is built) bought many years ago is reported at its value at the time, while the cost of such an asset today might differ greatly. Second, when an acquisition occurs, the assets of the acquired firm are reported on the balance sheet at their market value, rather than at their book value as they are on the balance sheet of the acquired firm (in accounting practices, the gap between the two is included in the category "goodwill"). While imperfect, the book value of assets remains the most accurate measure of a firm's size and such data can be easily obtained through firms' annual reports and balance sheets. Differential breadth will thus be measured here as "differential asset accumulation", namely as the evolution in the book value of assets.

Differential Asset Accumulation

By comparing the growth of assets for dominant pharmaceutical firms as compared with the growth of assets for dominant firms in other sectors, one can measure the growth in differential breadth for the pharmaceutical sector in historical perspective. Once again, no complete historical data are available for global firms while such data are available for American firms. The Fortune database allows one to compare the average growth of assets, measured by their book value, for dominant American pharmaceutical firms as compared to the average growth of assets for the 500 most important firms listed in terms of assets (Figure 5.2). The graph uses a log scale and is rebased on 100 starting in 1954 for both pharmaceuticals and all sectors in the United States.

Figure 5.2: Big Pharma Differential Asset Accumulation 1954-2004
Book Value of the assets of an average U.S. dominant pharmaceutical firm as compared to an average Fortune 500 firm (1954=100, log scale)



*: Until 1993, the Fortune 500 included only firms from the mining and manufacturing sector. Since 1994, the list includes firms from all sectors, causing an upheaval in data for that year due to the important financial assets for banks and investment funds. In order to eliminate this bias, 1994 numbers were rebased according to 1993 numbers.

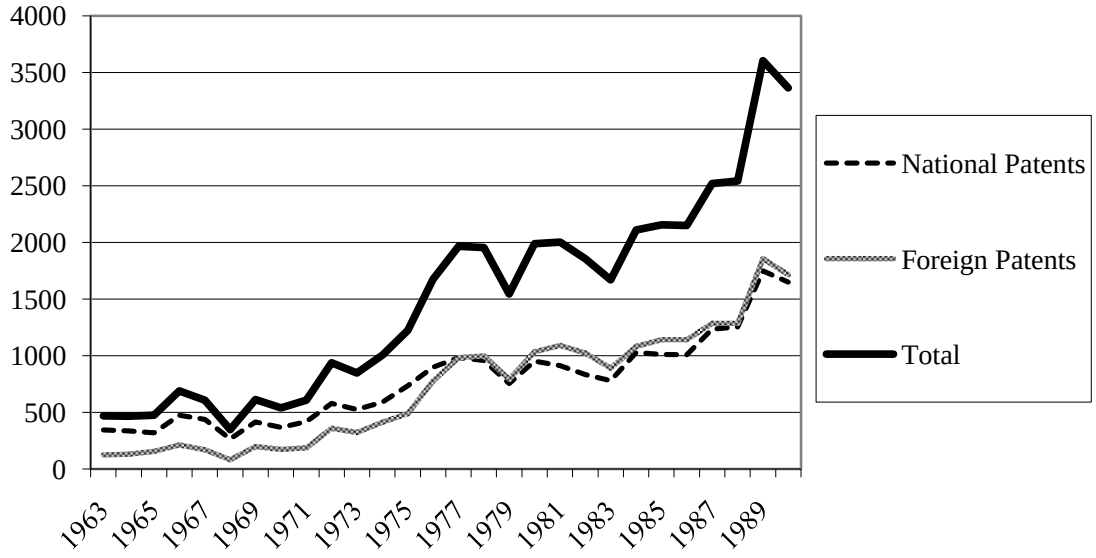
Source: Fortune

The differential asset accumulation for pharmaceutical firms can be the result of faster asset growth through greenfield investments or of faster growth through M&As. Figure 5.2 shows that the growth rate for dominant firms' assets in the pharmaceutical sector was more

or less the same as for other sectors until the mid 1960s. From there, the differential growth begins to accelerate for pharmaceuticals as compared to other sectors. The differential growth of assets from the mid-1960s to 1980 is not based on greater M&As in pharmaceuticals. During that period, historical data show that there was an important wave of M&As among American businesses during all the 1960s. According to *Historical Statistics of the United States* (U.S. Bureau of the Census 1975, 914), while there was an average of 425 mergers recorded every year in manufacturing and mining from 1946-1959 in the United States, this average jumped to 1266 between 1960 and 1970. In the case of pharmaceuticals, there were only four important M&As between the mid-1960s and 1980: Bristol-Myers bought Mead-Johnson in 1967, Warner-Lambert bought Parke-Davis in 1970, Schering and Plough merged in 1971 and SmithKline and French merged with Beckman Instruments in 1976.

In the pharmaceutical sector, the 1960s and 1970s are considered to be a period of important internal growth for dominant firms. Chapter 4 explained the reasons for such internal growth: 1) the great expansion of R&D activities since the 1950s; 2) tighter regulations and the emergence of RCTs in the 1960s (which increased production costs); and 3) the multinationalization of American dominant pharmaceutical firms in the 1960s and 1970s (which greatly increased FDI). The increased development of assets through R&D can be observed in the 1970s, with the number of pharmaceutical patents produced during that period, nationally and abroad (Figure 5.3). Note that the figure refers to all pharmaceutical patents and not only to patents obtained by dominant pharmaceutical firms, since these data are not available.

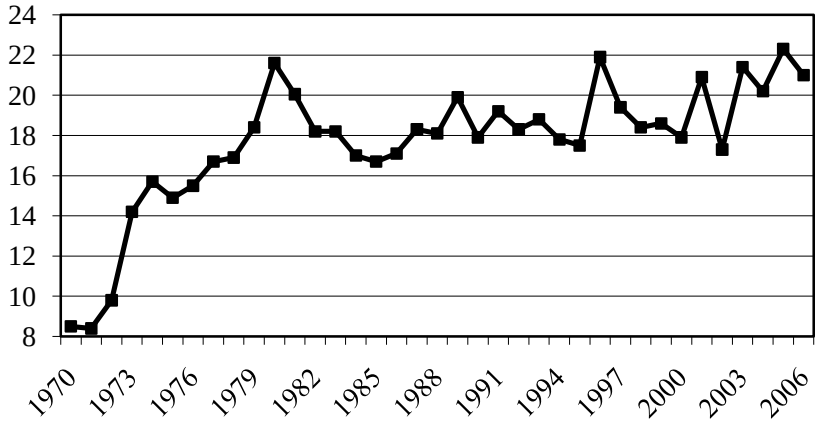
Figure 5.3: Pharmaceutical Patents Obtained by American Interests, 1963-1990



Source: USPTO

The trends show sharper growth in foreign patents, which is consistent with the idea that American pharmaceutical firms accelerated the internationalization of their activities in the late 1960s. Accordingly, the share of R&D abroad as a part of total R&D for American pharmaceutical firms went from 8.5% in 1970 to 21.6% in 1980 (Figure 5.4). The differential growth of assets between the mid 1960s and 1980 was thus due first and foremost to internal growth by increased R&D and greenfield investments, especially abroad. M&As did not play a significant role during that period.

Figure 5.4: R&D Abroad as a Share of Total R&D for PhRMA Members 1970-2006



Source: PhRMA 2007

The story is different in the 1980s. Figure 5.2 clearly shows acceleration in the differential growth of assets in the 1980s, while there is stagnation in patent grants (Figure 5.3). Further, the important greenfield investment abroad to internationalize pharmaceutical firms appears to be over, since we observe a stagnation in the ratio of R&D realized abroad to total R&D after 1980 for PhRMA members (Figure 5.4). In the 1980s, the growth in differential breadth was thus a different story, with two main characters: Biotech Boom and Merger Mania.

5.2 Biotech Boom: The Growing Supporting Nexus

In Chapter 2, it was mentioned that technological evolution in a sector could jostle around the power relations between vested interests within the existing knowledge structure.

The emergence of biotechnology and of "discovery-by-design"[60] in the 1970s provided some opportunity for new firms developing new technologies to challenge dominant firms and enter the realm of Big Pharma. Medical advances in the biochemical workings of cells, for example through the work of James Black (Black and Stephenson 1962), undergirded the hope that pharmaceutical firms would be able to design drugs to match defined functions. As such, biotechnology quickly became the new Grail in pharmaceuticals, promising a new era of discovery.

The results of this discovery strategy, however, have proven disappointing. In a study of 46 American biotechnology companies by Bayer in the mid-1980s (quoted by Redwood 1987, 318), the results were impressively poor: with 7904 employees, the firms had expenditures of $715.5 million and an income of $574.7 million, which meant losses of $140.8 million. In spite of massive state interventions in the United States to develop biotech by sequencing the human genome (Loeppky 2005), the results in biotechnology even today remain mostly disappointing (Pignarre 2003, 108-119; Wade 2008). As Daniel Vasella, CEO at Novartis, explains: "Investors begin to realize that we cannot do much from sequencing the human genome and that we will need many years before it allows the development of new medicines. The bubble has burst and this is where we are today" (Ducruet 2002, author's translation). The fatal conceit was that it was actually possible, in spite of the complexity of biology, to "know" enough to be able to achieve drug design, to make a chemical from the ground up and produce the desired effect on the human body. Our ignorance, however, is

[60] The "discovery by design", or "rational drug design" strategy is a method of discovery based on the systematical synthesizing of chemicals in order to directly produce the desired effect on the human body. The rationale for this new scientific approach is that if we can explain human disease from the most fundamental level of the cell through its genes and proteins, it should be possible to correct whatever is wrong (Le Fanu 1999, 248-9).

such that such a scientific approach to pharmaceutical innovation would not lead, even today, to the discovery of *Aspirin*, penicillin or cortisone. While, the pharmaceutical business sometimes blame the "dearth of new drugs" on over-regulation (Becker 2002; Epstein 2006), Le Fanu explains (1999, 250) that the problem runs deeper; it is the whole approach to drug discovery that should be questioned.

Whatever the ultimate results, however, since the mid-1970s biotechnology was perceived as the coming El Dorado to cure diseases, and the promises of such a technology transformed the supporting nexus of Big Pharma, with the emergence of many new players developing and exploiting those new technological capacities. The analysis of differential asset accumulation through internal growth allows us to understand the importance of this growing supporting nexus.

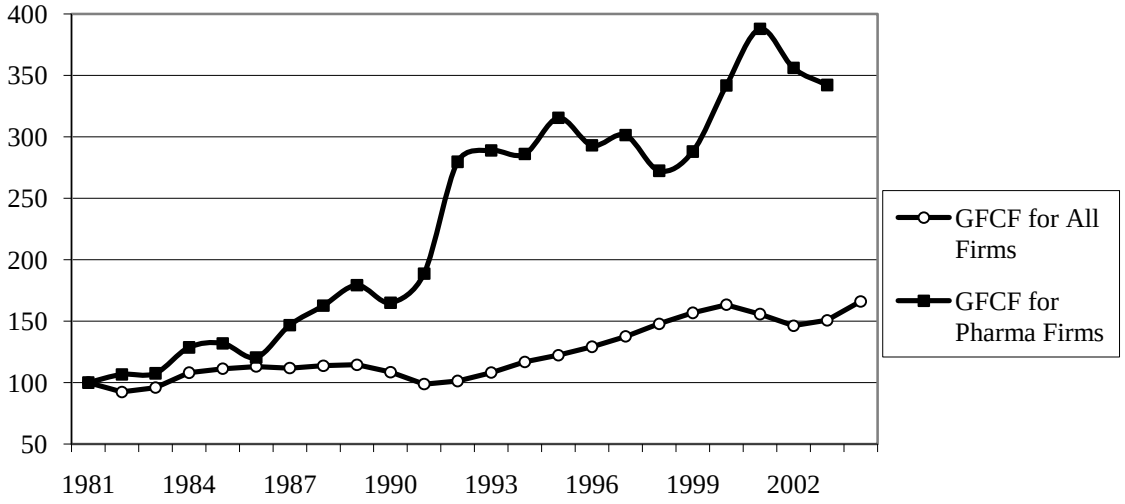
Differential Internal Growth: The Results

Differential asset accumulation is possible through internal growth (greenfield investments) or external growth (M&As). This distinction is important in terms of the impact of such asset accumulation on the accumulation regime for the sector. Internal growth entails the building of new productive capacities and, ultimately, creates more social wealth. External growth is different, since it means buying back existing productive capacities in order to rationalize it and integrate it with larger production facilities. External growth involves increasing the firms' earning-capacities by concentrating capital, by increasing monopolistic capacities and, most of the time, by reducing overall production. Internal

growth can be measured by the evolution of "gross fixed capital formation"[61] (GFCF). This section focuses on analyzing internal growth and the next one analyzes external growth. By comparing the evolution of GFCF for the pharmaceutical sector with other sectors, it is possible to measure differential breadth due to internal growth (Figure 5.5).

Figure 5.5: Differential Internal Growth for the American Pharmaceutical Sector

Real GFCF in Pharmaceuticals and in All Sectors 1981-2004 (1981=100)



Sources: OECD Health Data 2007; Statistical Abstract of the United States (various years)

One can observe two clear surges in differential internal growth for the pharmaceutical sector from 1986 to 1992 and from 1998 to 2001. Note that between 1995 and 1999, during the peak of what was called the "New Economy", the GFCF has declined in pharmaceuticals to a level lower than in 1993. Overall, the graph seems to show that very important

[61] Gross fixed capital formation includes the growth and the replacement of used fixed capital (depreciation). Real gross fixed capital formation is adjusted for inflation using the Consumer Price Index for all Urban Consumers.

productive investments and, thus, differential internal growth appeared in the 1980s in the pharmaceutical sector, which should explain that profits increased in pharmaceuticals because of greater investments. However, the story becomes completely different as soon as we discriminate between Big Pharma and its supporting nexus.

As explained in Chapter 2, the pharmaceutical business is made up of dominant firms with a supporting nexus of small and medium-sized firms. The differential accumulation in terms of internal growth observed in figure 5.5 applies to the whole U.S. pharmaceutical sector, including dominant and smaller firms. There are clearly two periods of intense positive differential accumulation in terms of GFCF: 1990-1992 and 1998-2001. An important anomaly, however, is that we do not find such a surge in GFCF for dominant pharmaceutical firms during those periods. While GFCF in all pharmaceuticals increased by 82% in nominal value between 1990 and 1992, an analysis of dominant firms' financial reports for this period shows that their investments in property and equipment increased only by 30% (Lauzon 1993, 14). For the period 1998-2001, GFCF in all pharmaceuticals increased by 55% in nominal value while dominant firms' financial reports show that the book value of equipment and property increased only by 13% (Lauzon and Hasbani 2006, 38). In both cases, the conclusion is that GFCF investment and internal growth in pharmaceuticals are not the result of an investment surge by dominant pharmaceutical firms but, instead, the result of an investment surge by non-dominant pharmaceutical firms constituting the supporting nexus. Moreover, the figures show in fact that differential accumulation for dominant pharmaceutical firms is not achieved by internal growth, in spite of important GFCF formation in that sector. Differential asset accumulation for American Big Pharma can thus only be the result of external growth (M&As). However, the nature of

the surge in GFCF in pharmaceuticals has its importance, because, otherwise, it is impossible to understand how M&As got its importance for Big Pharma.

The Biotech boom since the late 1970s is central in understanding the numbers for GFCF in pharmaceuticals. Many factors caused this boom. The "Discovery-by-Design" strategy developed in the 1970s surely was central to it, but the Bayh-Dole Act of 1980, which encouraged patenting of federally funded research, accelerated the rise of start-up biotech firms, often based on publicly funded academic research. Also, as Fabienne Orsi (2001) correctly points out, the reshaping of financial markets in the United States in order to favor venture capital helped financing the emergence of new firms in pharmaceuticals in the 1980s, especially for the period prior to the 1987 crash that made equity capital much less available for small companies (OTA 1991, 51-52). However, contrary to the assertion of advocates of the New Economy thesis, the rise of biotech firms does not signal the rise of dynamic competitors to the old dinosaurs of Big Pharma. Instead, most biotech firms were entirely dependent upon Big Pharma. For example, Rodney Loeppky (2005, 80) explains that "by 1988, over 400 biotechnology firms had emerged with supporting funds from over 70 major corporations". The OTA (1991, 51) confirms Loeppky's analysis by observing that by the late 1980s, 75% of biotech firms did not rely on public equity for their financing but, instead, preferred to rely on corporate funds and strategic alliances with major firms. The large majority of biotech firms never managed to develop their own organizational capabilities (OTA 1991, 55):

> The original intent of many of the early [dedicated biotechnology companies] was to become fully integrated, competitive pharmaceutical companies, but the economics of the pharmaceutical industry may very well deny this opportunity to most. Perhaps in recognition of those barriers, many of the newer companies were founded with the intention of developing

> one idea or targeting a niche market and, perhaps, being acquired. [...] According to a recent Ernst and Young survey, 39 percent of all companies surveyed expect to be acquired by a large firm within the next 5 years, and 32 percent expect to merge with an equal-size firm in the same period.

The analysis must thus turn here to the articulation between the biotech boom and Big Pharma's strategy. For some authors, the way to explain the multiplication of biotech firms in the supporting nexus of Big Pharma would be that dominant pharmaceutical firms depended more and more on biotech firms in order to feed their pipelines. According to this point of view, Big Pharma has externalized its R&D to the supporting nexus, but in such a way as to maintain its control through different alliances. For example, since the early 1980s, one can observe increasing cooperation and alliances between firms (Gambardella 1995; Danzon et al. 2003), increasing in-licensing of molecules by dominant firms (DiMasi 2000) and outsourcing of R&D and production by dominant firms with increasing use of Contract Manufacturing Organizations (CMOs) and Contract Research Organizations (CROs) (Flavin et al. 2001). The growth in pharmaceutical GFCF surely is the result of growing R&D externalization for Big Pharma. Externalization, however, must not veil here the control that was maintained by Big Pharma over this supporting nexus, and how dependent the latter remained in its relationship to Big Pharma. As we will see, externalization and integration are the two faces of the same coin that constituted the new accumulation regime, producing differential growth for Big Pharma since the 1980s. The existing barriers to entry in pharmaceuticals usually caused a general incapacity for new biotech firms to challenge dominant firms. As an important technological breakthrough for pharmaceutical innovation, biotech became a technological imperative without which a dominant firm would lose its preeminence over others. But, even though Big Pharma was not well-fitted to develop this

technology, biotech had to be carefully tamed, such that it would serve Big Pharma's earning-capacity.

A New Division of Labor in Pharmaceutical Innovation

The Biotech boom, with its multiplication of new biotech firms, did not contribute to the emergence of competition but, rather, to the consolidation of the control exercised by Big Pharma over the industry. Start-ups, as well as small and medium-sized pharmaceutical firms, strengthened the supporting nexus of Big Pharma and became the feeding ground from which dominant firms could simply buy back any promising research for future compounds. Small biotech firms were better adapted to exploit the new technologies that surfaced with the growing understanding of DNA, but most of them never managed to develop their own organizational capabilities and, as a consequence, depended for their earning-capacity on alliances with dominant firms.

This state of affairs is not surprising, since high barriers to entry were already constituted before the 1980s. The emergence of discovery-by-design as a new industrial model for therapeutic innovation necessitated more upstream research for which Big Pharma is usually less suited than smaller firms. Dominant firms have important comparative advantages in large-scale product development and marketing of innovations, but smaller groups, especially the ones linked with academic research labs, are more efficient for upstream research (Arrow 1983; Scherer and Ross 1990; Sylos Labini 1992). For example, Gambardella (1995, 76) explains the comparative advantages of small and dominant firms:

> Big firms have large organizations, which are critical for systematic product and process development, and they have extended commercialization assets. They also face lower capital costs. A reason for this is that they can resort more extensively to internal funds. Small firms cannot finance large-scale development projects internally, and they have to borrow. In innovation, moral hazard is severe, and capital markets command a premium. Moreover, large firms face a lower cost of external capital, as they can spread uncertainty over a large number of activities (and innovation projects), and more generally their solvency is less at risk. But the flexible and informal organizations of small groups facilitate invention and the production of ideas.

Gambardella's conclusion is that this state of affairs creates a division of labor in innovation between the group of dominant firms and its supporting nexus. One needs to keep in mind, however, that Big Pharma, to an important degree, directly organized this division of labor for its own interests. Big Pharma has externalized innovation, but remains, most of the time, the mandatory pathway for bringing innovations to the pharmaceutical market. Koyin Chang has defended this conclusion regarding the organization of the R&D intensive firm (quoted in Loeppky 2005, 69):

> Although not the intention of the [new biotechnology firms (NBFs)] founders, the biotechnology industry, in its early years, took on the characteristics of a specialised R&D supply sector. Indeed, it could be argued that the biotechnology industry emerged as a market for R&D, with NBFs on the supply side and established chemical and pharmaceutical enterprises on the demand side.

With this structural reorganization of the sector, the rise of new technologies did not involve the emergence of new competitors challenging the old cartelized dominant firms; it simply consolidated the cartel's control over the whole sector, by externalizing R&D costs while keeping at reach any promising results. This general control can be observed through the important networks of agreements that were organized between dominant pharmaceutical firms and smaller firms (mostly biotech) in the 1980s. The cooperation agreements were

based on research collaboration, licensing agreements, marketing agreements, joint ventures and the like. Table 5.1 shows that the strategy of alliances and agreements were the same for dominant American firms like Merck and Pfizer and for dominant foreign firms, such as Ciba-Geigy and Hoffmann La Roche. Those networks of agreements are presented in more details by Gambardella (1995).

Table 5.1: Networks of Agreements with Biotech Groups for Four Representative Dominant Pharmaceutical Firms, 1984-1992

Dominant Firms	Networks of Agreements
Ciba-Geigy (now part of Novartis)	Affymax; Agricultural Genetics; Agri-Diagnostics; ALZA; Aphton; Applied Microbiology; Biogen; Biosys; Calgene; Chiron; Collaborative Research; Genencor; Genentech; ISIS Pharmaceuticals; North Carolina Biotechnology Center; Noven. Pharmaceuticals; Panlabs; Plantorgan; Tanox Biosystem
Hoffmann La Roche (now Roche)	Ajinomoto; Immunex; Alpha 1 Biomedicals; Amgen; Angenics; Biogen; Boehringer Ingelheim Vetmedica; Chiron; Cortecs; Dainippon Pharmaceutical; Genentech; Genica Pharmaceuticals; Genzyme; Immunomedics; Interferon Sciences; Metpath; Protein Design Labs; SangStat Medical; Scios; Summa Medical; Syntex; Xenova; XOMA.
Merck	AB Astra; ALZA; Behringwerke; Biogen; Celltech Group; Chiron; Immulogic Pharmaceutical; Immunetech Pharmaceuticals; Imperial Cancer Research Technology; INBio; MedImmune; Panlabs; Repligen; Shionogi; Singapore Biotechnology; Biologicals S.A.; Syva; Vical.
Pfizer	Advanced Polymer Systems; ALZA; Celltech; Collaborative Research; Ecogen; Genzyme; Ligand Pharmaceuticals; The Liposome Co.; Microvascular Systems; MPS (IGI); Moleculon; Natural Product Sciences; Neurogen; Oncogene Science; Petroferm; Scios; XOMA.

Source: Bioscan; Gambardella (1995)

Cooperation agreements were the main way to organize the division of labor between innovation, development and commercialization in the 1980s. However, venture capital became more and more difficult to obtain in the late 1980s due to the stock market crash. Thus, strategic alliances and direct acquisition of smaller groups became the rule in the 1990s, as we will observe by analyzing external growth. In any case, the multiplication of new pharmaceutical firms did not encroach in any way Big Pharma's earning-capacity, since dominant firms maintained their grip on those newcomers all along, through multiple alliances and agreements. On the contrary, the index in terms of differential accumulation clearly shows how Big Pharma consolidated its control over the sector since the middle of the 1980s (Figure 5.1).

This general trend, however, is not free of exception. For example, Amgen, founded in 1980, managed to become a core company by developing its own organizational capabilities. The giant Wyeth still owns today 10% of Amgen shares and certainly has much influence in the management of the firm, but Amgen must now be considered to be an independent firm that managed to enter the realm of Big Pharma through the technological opportunity offered by biotech and the appropriation of public research on Erythropoietin (EPO) (Goozner 2004, 13-38). Genzyme is another biotech firm that made it alone, but it is still too small to be considered part of Big Pharma. Nevertheless, most other important biotech firms, such as Genentech, Chiron, Immunex, Syntex and Genetics Institute, followed the general trend, and are now subsidiaries of dominant firms.

Note that the U.S. state has been encouraging such restructuring of the division of labor in pharmaceutical innovation, not only by promoting the commodification of public research

to facilitate the transfer of its results to private firms, but also by funding directly biotech capabilities, for example through the Human Genome Project. As Loeppky (2005) explains, the industry greatly benefited from the Human Genome Project, a state-led initiative that socialized risks and costs for the mapping of the human genome, in order to develop innovation capabilities in genetics for private firms. The state acted as the public sponsor of a technological capacity that was developed mostly in university laboratories and national laboratories between 1988 and 2003, but the technological results were to be transferred at no cost to private firms (mostly American), in order for them to consolidate their technological advantage. The state thus provided a "technological fix" for a national industry considered to be losing its competitive edge in the global markets. As Loeppky (2005, 103-106) explains, in the Senate Hearings on genetics, "policymakers demonstrated their concern, almost obsession, with the possibility that U.S. competitiveness was suffering at the hands of foreign competitors". The idea was simple: America must help its firms to remain dominant in the pharmaceutical sector. For example, Jack McConnell, the corporate director of advanced technology for J&J, assisted in drafting the first Congressional bill regarding the Department of Energy's proposal for a Human Genome Initiative. His reasons for supporting the idea of mapping the genome were straightforward (quoted in Loeppky 2005, 81):

> If we want the U.S. to maintain its position as a dominant force in the pharmaceutical industry in the world, I cannot imagine our letting this opportunity pass by us. Someone has said that the group that first gains access to the information from mapping and sequencing the human genome will be in position to dominate the pharmaceutical and biotech industry for years to come.

In any case, the economic advantages for American interests were central to the decision to fund the Human Genome Project throughout the 1990s. The technological opportunity offered by genomics had to be tamed in a way that consolidated the existing vested interests of American Big Pharma. According to the U.S. Department of Energy, the U.S. government thus spent $ 4.3 billion (in constant 2003 dollars) between 1988 and 2003 to map the human genome, and the results were made freely available to private firms. The Human Genome Project was completed in 2003.

The restructuring of the division of labor in pharmaceutical innovation in the United States also meant a restructuring of Big Pharma itself: prevalent organizational capabilities necessary for dominant firms were evolving to stress product development and marketing over research. This trend modified the relationships of power among U.S. Big Pharma according to each firm's organizational capabilities. Since the restructuring of the U.S. innovation system soon became the model worldwide, global Big Pharma needed to adapt to this transformation. The firms that did not focus on the new strategic organizational capabilities or that did not develop their own networks of alliances, cooperation and research agreements would lose control and power over the rapidly evolving industry. Declining firms became easy prey for the remaining dominant firms that wanted to develop their own capabilities by acquiring external capacities. The result was a series of M&As, even among dominant firms, which increased the concentration of capital through external growth.

5.3 Merger Mania: Enter the New Accumulation Regime

As the supporting nexus continued to grow with the help of Big Pharma, the latter maintained its control over the whole sector through its capacity to buy back any promising result that emerged from this nexus. Mergers and Acquisitions (M&As) were central in maintaining this dominance. The wave of M&As that began in the 1980s changed the face of Big Pharma although, interestingly, it did not emerge from the United States. On the contrary, antitrust laws were so decisive in the U.S. that they greatly restrained M&As. The wave began abroad, but then forced the loosening of the U.S. antitrust laws, as a means to "compete" against corporate concentration abroad. The cause of the M&As wave that appeared in the 1980s must be understood within an institutional context that had previously restrained such a wave.

Antitrust versus Big Business

Antitrust activity and anti-big-business sentiment increased considerably with the misfires of the Roosevelt's New Deal's recovery program in the 1930s, which allowed a minor strain of thought, greatly influenced by the works of Thorstein Veblen, to emerge in policy-making circles. According to this strain of thought, the Depression was nothing more than a "strike of capital" to curb "overproduction", and massive unemployment was due to the misuse of power by big business (Hounshell and Smith 1988, 346). Some of Veblen's disciples, like Rexford Tugwell and Adolf Berle became leading members of Roosevelt's brain trust, and Felix Frankfurter, one of Veblen's admirers, often identified as a radical, was appointed by Roosevelt as a Justice of the Supreme Court in 1939. The one who had the most

impact in trustbusting under Roosevelt was Thurman Arnold, another of Veblen's disciples. Arnold was appointed as Assistant Attorney General in charge of the Antitrust Division from 1938 to 1943. He managed to beef up the Antitrust Division by increasing the number of lawyers from 48 to over 300 in the first two years of his appointment (Gressley 1964, 224). Under his direction, the Antitrust Division undertook in five years 215 investigations and instituted 44% of all the proceedings under antitrust laws undertaken by the Justice Department since the implementation of the Sherman Antitrust Act in 1890 (Miscamble 1982, 5). Arnold attacked, among others, technology-based big businesses. In his testimony before the Senate Committee on Patents in 1942 (quoted in Hounshell and Smith 1988, 346-347), he argued that cartels had found refuge under the patent laws and that defensive patents (or patent thickets) were a typical abuse of power. The Supreme Court also moved to strengthen the trustbusting assault. It abandoned the "rule of reason" as a guiding principle for antitrust action in favor of a new doctrine, which defined the existence of monopoly when "power exists to raise prices or to exclude competition when it is desired to do so" (American Tobacco Co. v. United States 1946). Such an interpretation of the Sherman Act meant, for example, that patents and processes agreements, such as the ones between DuPont and ICI, would become illegal and would be put to an end by authorities (Hounshell and Smith 1988, 346).

Facing such antitrust hostility, strategies for business consolidation and monopolistic power by restraining competition were under scrutiny, and M&As were highly suspicious. American authorities forced the dismantling of cartels like I.G. Farben and Basel AG in the 1950s in the name of competition. When patent litigations led to the creation of a cartel in broad-spectrum antibiotics through patent pooling in the 1950s, an immediate investigation

was launched into the business practices in this sector and a federal suit followed.[62] Big Pharma, however, had an important argument to counter the zeal of trustbusters: pharmaceutical innovation was strong and new important medicines were arriving steadily on the shelves of pharmacists. With the emergence of the regulatory system based on costly RCTs in the 1960s and 1970s, however, a more important share of me-too drugs were being introduced, instead of major innovative discoveries, in order to reduce costs. The lack of important discoveries in the late 1970s not only brought an atmosphere of pessimism among pharmaceutical firms, but also a growing popular discontent among their critics. Trends seemed to confirm Senator Kefauver's depiction of the GPB according to which patents sustained predatory prices, marketing expenditures were too high and new drugs did not show enough therapeutic benefit (Kefauver 1965, passim). While the antitrust sentiment was not in itself a challenge to Big Pharma, it meant that any attempt to consolidate the industry even more through anticompetitive practices would entail an important ideological struggle to justify such actions.

Until the end of the 1970s, U.S. antitrust authorities were eager to impede the M&As of American firms, in order to restrain concentration and cartelization. Authorities accepted some M&As but tended to retard them. For example, the merger of the two American pharmaceutical firms Parke-Davis and Warner-Lambert in 1970 was delayed for almost seven years due to antitrust concerns (Pharmaceutical Panel CTIETI 1983, 79). Pharmaceutical firms in Europe, in contrast, began to accelerate their M&As in the 1970s through important deals allowed by their respective governments. Europeans needed to

[62] As Temin notes (1979, 440n), the drug firms involved in the cartel, such as Lederle and Pfizer, were ultimately not found to have violated antitrust laws in 1970 and 1972. Their first conviction was reversed on appeal and the Supreme Court maintained the reversal. The firms nevertheless paid $200 million in different private settlements during the 15 years that the criminal suit was in progress.

accelerate their path to globalization in order to compete with American firms. For example, the Swiss firms, Ciba and Geigy, merged in 1970; the German firm Hoechst acquired a majority shareholding in French Roussel-Uclaf in 1974; German BASF acquired the German Knoll in 1975; German Bayer acquired the American firms Cutter Labs in 1974 and Miles Labs in 1978. Also, in 1973, the French government created its own national champion in pharmaceuticals, Sanofi, by merging several healthcare, cosmetic and animal health companies into a subsidiary of the state-owned oil company ELF-Aquitaine. Another French champion, Synthélabo, was set up in 1973 under L'Oréal's control after a series of acquisitions.

Foreign countries were creating national champions by allowing the development of their dominant pharmaceutical firms. By 1980, the most active players in M&As, Hoechst, Bayer and Ciba-Geigy, were, respectively the first, second and third largest pharmaceutical firms on the planet. This state of affairs became a cause for alarm for American authorities, especially when dominant firms abroad began to directly buy out American firms. The existing American antitrust laws did not prevent the acquisitions of small and medium sized U.S. firms by large foreign multinationals, since antitrust authorities could only hamper M&As between U.S.-owned firms. Dominant foreign firms, including pharmaceutical firms, were thus involved in an acquisition rampage in the 1970s for small and medium-sized American firms in order to better penetrate the U.S. market (Table 5.2).

Table 5.2: Main Acquisitions by Dominant Foreign Firms of American Pharmaceutical Firms in the 1970s

Dominant Foreign Firm	U.S. Firm acquired	Year of Acquisition
Hoechst (Germany)	Calbiochem Corp	1977
Bayer (Germany)	Cutter Labs Miles Labs Dome Labs	1974 1978 1978
Ciba-Geigy (Switzerland)	Alza	1977
Glaxo (U.K.)	Meyer Labs	1977
Sanofi (France)	Towne Paulsen Western Research Labs	1975 1976
Rhone-Poulenc (France)	Norwich-Eaton (10.5%)	1978
Schering AG (Germany)	Berlex Labs	1979

Source: Pharmaceutical Panel CTIETI (1983, 48).

By the end of the 1970s, the main European competitors thus had important access to the American market, and so the protection previously offered by the "drug-lag" mentioned in Chapter 4 no longer existed. Hoechst, Bayer and Ciba-Geigy managed, in fact, to restore their interwar positions within the American prescription drug market (Chandler 2005, 294). This threat to U.S. competitiveness from foreign corporate Behemoths, combined with the anti-regulatory ideology of the Conservatives who took control of Congress in 1980 with the election of Ronald Reagan, occasioned U.S. antitrust authorities to relax their antitrust concerns over the M&As of domestic firms. For example, the U.S. antitrust authorities codified its more permissive approach in the Antitrust Division's Merger Control Guidelines

of 1982 (Sell 2003, 72). In the 1980s, we thus observed a surge in major M&A activity among U.S. firms (Table 5.3).

Table 5.3: Main M&As by Dominant American Firms in the Pharmaceutical Sector in the 1980s

Transaction involved	Year of M&A
Dart Industries merges with Kraft	1980
Dow merges with Richardson-Merrell	1981
Merck acquires Banyu (Japan)	1982
Procter and Gamble acquires Richardson-Vicks	1985
Monsanto acquires G.D. Searle	1985
Marion Laboratories merges with Merrell-Dow Pharmaceuticals	1987
Eastman Kodak acquires Sterling Drugs	1988
SmithKline Beckman merges with Beecham (UK)	1989
Bristol-Myers acquires Squibb	1989

Sources: Chandler (2005), Derdak (various years) and Hoover & al. (various years).

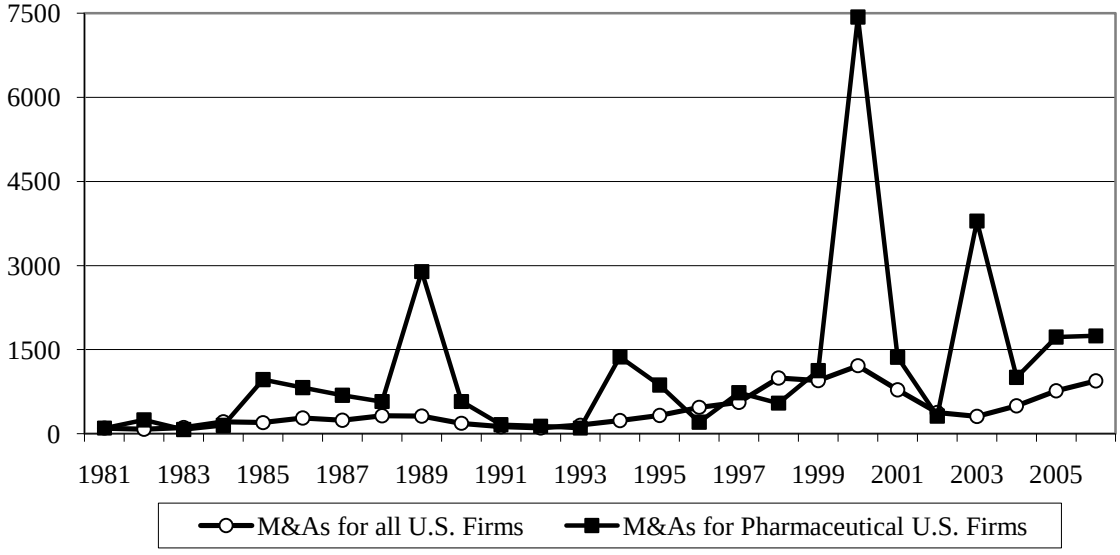
It thus seems that M&As became central in Big Pharma's ongoing business model in the 1980s. To prove this point, it is first necessary to measure the importance of M&As, and then find the rationale behind the importance of M&As, and how they contribute to Big Pharma's business model.

Differential External Growth : The Results

In his dissertation on the productivity crisis in pharmaceuticals mostly caused by (and conducive to) M&As, Lavigne (2006, 35-6) shows that while dominant firms rely more and more on their supporting nexus, this does not mean a greater general outsourcing of pharmaceutical activities. While there is a real trend towards outsourcing and externalization, there is a countervailing trend in terms of the integration of external resources for Big Pharma. The articulation between dominant firms and their supporting nexus in the 1980s can be better understood by looking more closely at M&As. Figure 5.6 shows the evolution of the value of external growth, or M&As, for American pharmaceutical firms and all American firms from 1981 to 2006.

Figure 5.6: M&As for Pharmaceuticals and All Firms

Real Value of M&As in the United States, 1981-2006 (1981=100)

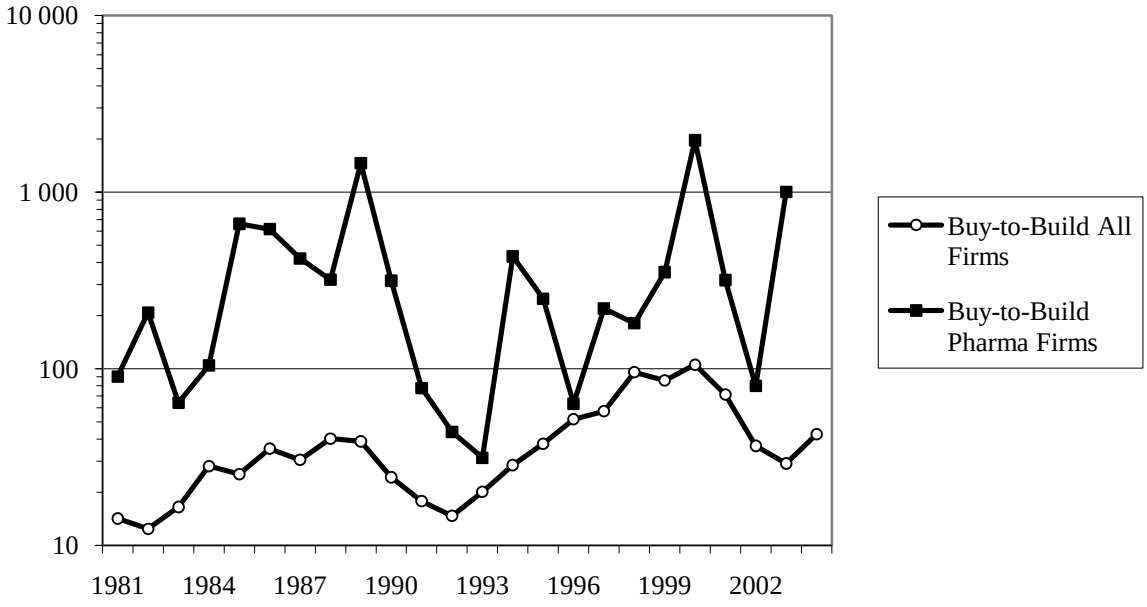


Source: Thomson Financials; Bureau of Labor Statistics

While Antitrust laws were relaxed for all sectors, figure 5.6 clearly shows an important differential external growth for pharmaceuticals as compared to other sectors from 1985 to 1990. The trends in pharmaceuticals and other sectors do not differ considerably from 1990 to 1999, except for the greater volatility in the pharmaceutical sector. Positive differential breadth appears again after 2000 in terms of M&As for pharmaceuticals. The trends in pharmaceuticals and other sectors, however, begin to differ considerably if we compare GFCF with M&As. In their works, Bichler and Nitzan propose to compare internal growth with external growth by comparing the ratio between the value of M&As and the value of "productive" investments as determined by GFCF. They call this standard the "Buy-to-Build Ratio" (Nitzan and Bichler 2002b, 54, 82-83), where a ratio of 50% would mean that for every dollar spent in building new tangible assets (GFCF), 50 cents would be spent in buying already existing assets (M&As). In the case of pharmaceuticals we clearly observe how dominant M&As are over GFCF (Figure 5.7).

Figure 5.7: Buy-to-Build Ratio

Value of M&As in Proportion to Gross Capital Formation for U.S. Pharmaceuticals and All U.S. Sectors, 1981-2004 (log scale)

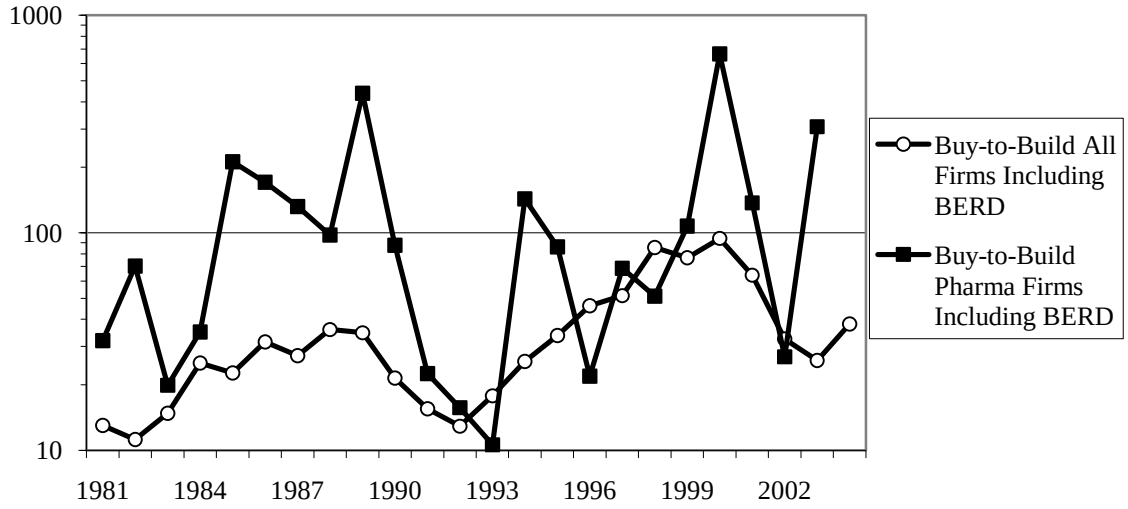


Sources: Bichler and Nitzan (2002b)
M&As for pharmaceuticals and all sectors: Thomson Financials (all U.S. targets)
GFCF for all sectors: Statistical Abstract of the United States
GFCF for pharmaceuticals: OECD Health Data 2007

In their works, Nitzan and Bichler (2002b, 54), show that the average Buy-to-Build Ratio for all American firms between 1895 and 1980 was, year in, year out, about 5%. In other words, for each dollar spent in "productive investments" (GFCF), only 5 cents was spent in M&As in order to buy back already existing "productive capacities". Then, between 1981 and 2004, the average "Buy-to-Build Ratio" jumped to 40% for all American firms and up to 61% in the ten years between 1995 and 2004. In the case of pharmaceuticals, the average "Buy-to-Build Ratio" achieved the high score of 403% for the period 1981 to 2003 (492% for the period 1995 to 2003).

Advocates of the New Economy thesis might assert that the problem with the Buy-to-Build ratio is that "productive investments" are here confined to GFCF, whereas intangible assets, such as patents or intellectual capital are not included in GFCF. The results and trends, however, are the same if we include all business expenditures in R&D (BERD) as part of GFCF, even without discounting tax credits for R&D, which usually turn around 50% of BERD depending on state legislation. The only overall difference is that the ratios are slightly lower in each case (Figure 5.8).

Figure 5.8: Buy-to-Build Ratio Including Business Expenditures in R&D
M&As in proportion to Gross Capital Formation for US Pharmaceuticals and All US Sectors, 1981-2004 (log scale)



Sources: Bichler and Nitzan (2002b)
M&As for pharmaceuticals and all sectors: Thomson Financials (all U.S. targets)
GFCF for all sectors: Statistical Abstract of the United States
GFCF for pharmaceuticals: OECD Health Data 2007
R&D for pharmaceuticals and all sectors: ANBERD (OECD)

When BERD is included, we observe that, between 1981 and 2004, the average "Buy-to-Build Ratio" was 36% for all American firms and up to 55% in the ten years between 1995 and 2004. In the case of pharmaceuticals, the average "Buy-to-Build Ratio" amounted to 129% for the period 1981 to 2003 (163% for the period 1995 to 2003). While complete data are not available yet for pharmaceuticals after 2003, all signs show that we continue to break new records (Young 2008; Economist 2008a). Those numbers not only show how central M&As became for pharmaceuticals, but also bluntly show that the driving forces for capital accumulation in the late XXth Century have little to do with the increase of productivity. Investments for greater earning-capacities translate less and less into building more productive capacities and more and more into extending control over already existing productive capacities. The situation is even more acute for pharmaceuticals. The break between productivity and profitability could not be here more obvious, and the Veblenian approach to capitalism could not be more relevant.

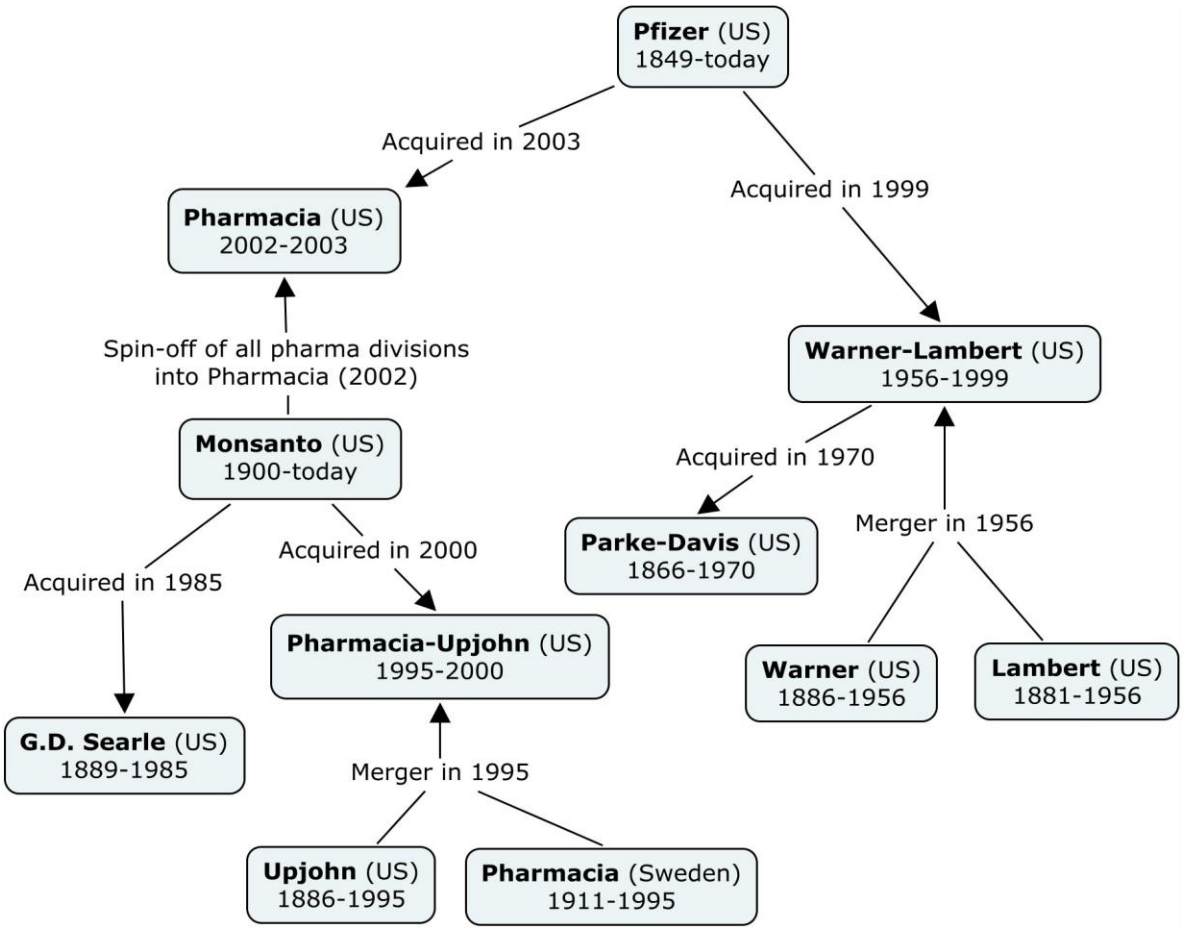
The analysis of differential internal and external growth allowed the observation of an important dynamic at work between Big Pharma and its supporting nexus, which greatly grew in the 1980s with the Biotech Boom. While Big Pharma externalized its R&D, in particular for biotech, it kept the upper hand by systematically buying back firms that might have had promising compounds or obtained strategic patents. The surge in GFCF caused by the Biotech Boom was in fact overwhelmed by the merger mania.

5.4 Merging Giants: The New Face of Big Pharma

The quantitative importance of M&As since 1981 cannot be explained only by the acquisition of smaller firms by Big Pharma, because that would leave out the importance of mergers among Big Pharma members. The transformations of the pharmaceutical sector that began in the early 1980s also saw winners and losers among Big Pharma firms. For example, such transformations were strongly beneficial to dominant firms focusing on brand-name pharmaceutical products with significant capabilities in product development and marketing. The OTC business model or the diversification strategy towards new types of products, became much less profitable and forced some giant firms to acquire complementary capabilities in new technologies. Strategic alliances, M&As became essential corporate strategies among Big Pharma firms to maintain their edge in the sector. Firms unable to keep pace faced disaster. For example, Eastman-Kodak, a chemical firm without strong R&D or marketing capabilities for pharmaceuticals, attempted to enter the realm of Big Pharma in 1988 by acquiring Sterling Drug, a dominant firm focused on OTC drugs. Because Eastman-Kodak did not develop capabilities in the new emerging technologies and attempted to continue with the old business model in pharmaceuticals, it simply ran into a wall: its net income plummeted from $1.4 billion in 1988 to $0.5 billion in 1989 and to $0.017 billion in 1991. Eastman-Kodak decided to sell off its pharmaceutical division in pieces in 1994 (Chandler 2005, 235). Adverse selection was thus at work even among Big Pharma firms. A number of these firms preferred to merge together to develop and adapt their organizational capabilities to the new environment, rather than face hostile take-overs by other dominant players.

The corporate family trees of dominant pharmaceutical firms tell us a lot about the power struggle among Big Pharma players for consolidation and survival. For example, Pfizer managed to become the world's most important pharmaceutical firm in terms of capitalization in recent years by massive external growth through mega-acquisitions of other dominant firms (Figure 5.9).

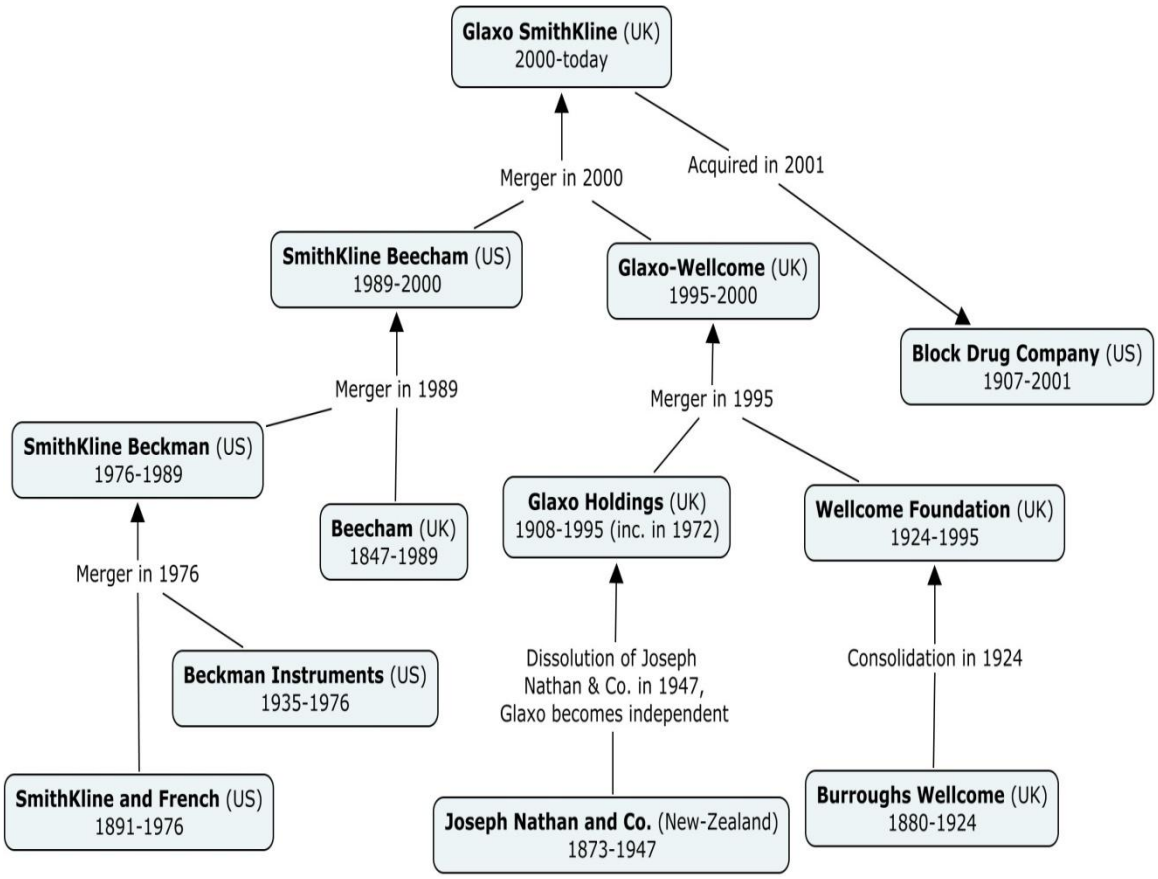
Figure 5.9: Pfizer's Corporate Family Tree



Sources: Pfizer's corporate website; Chandler (2005);
Derdak (various years); Hoover & al. (various years).

In the United States, other important deals were the mergers between Bristol-Myers and Squibb in 1989 and the acquisition of American Cyanamid by American Home Products (now Wyeth) in 1994. Another aspect of this merger mania was that it was not confined to American dominant firms. Foreign firms followed suit for three main reasons. First, many mergers took place among national firms, such as those in England, France, Germany and Switzerland, in order to build up national champions against the new American giants. Second, many mergers took place between foreign firms and American firms in order to build up strategic global marketing capabilities. Third, foreign firms acquired many American biotech firms in order to build up their strategic networks in the new biotech technology, which had been mostly developed in the United States. For example, in England, Glaxo Holdings merged with the Wellcome Foundation in 1995 to create the national champion Glaxo-Wellcome, while the British giant Beecham merged with the American giant SmithKline Beckman in 1989 to develop mutual marketing capabilities. SmithKline Beecham merged in 2000 with Glaxo-Wellcome to consolidate the national champion while at the same time acquiring the American Block Drug Company. The resulting giant, GlaxoSmithKline, is now the third most important pharmaceutical group on the planet after Pfizer and Johnson and Johnson in terms of capitalization (Figure 5.10).

Figure 5.10: GlaxoSmithKline's Corporate Family Tree

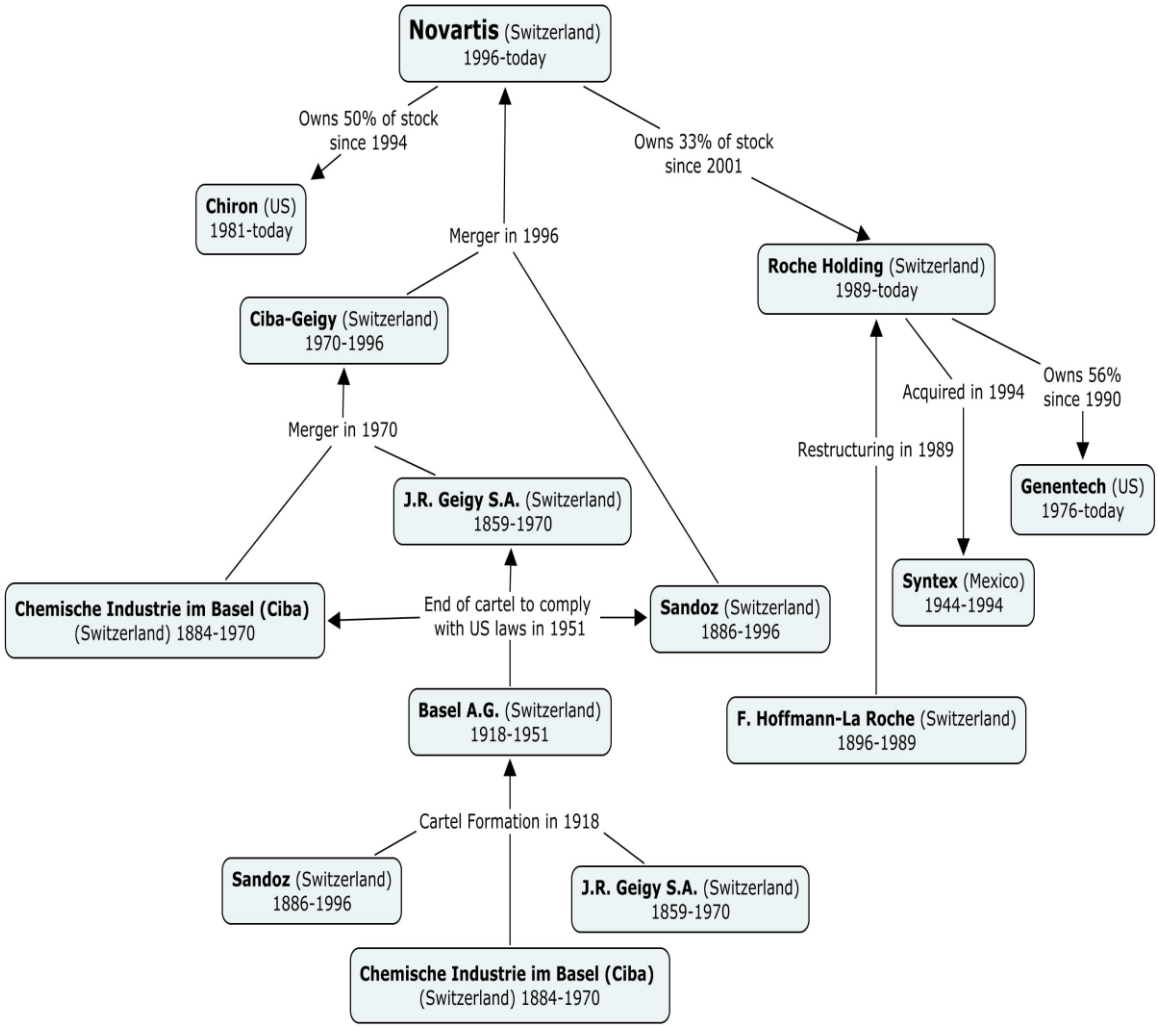


Sources: Firms' corporate website, Chandler (2005), Derdak (various years) and Hoover & al. (various years).

In the Swiss case, things were rather extreme. Mergers permitted the re-creation of the pharmaceutical cartel Basel AG, with the creation of the Swiss super-giant Novartis. Novartis then acquired a third of Roche (formally autonomous of Novartis since the Roche family holds the majority of its shares), and also acquired the American biotech Chiron. Roche acquired the biotech Syntex and Genentech. The giants Roche and Novartis are now

the world's fourth and fifth most important pharmaceutical groups in terms of capitalization (Figure 5.11).

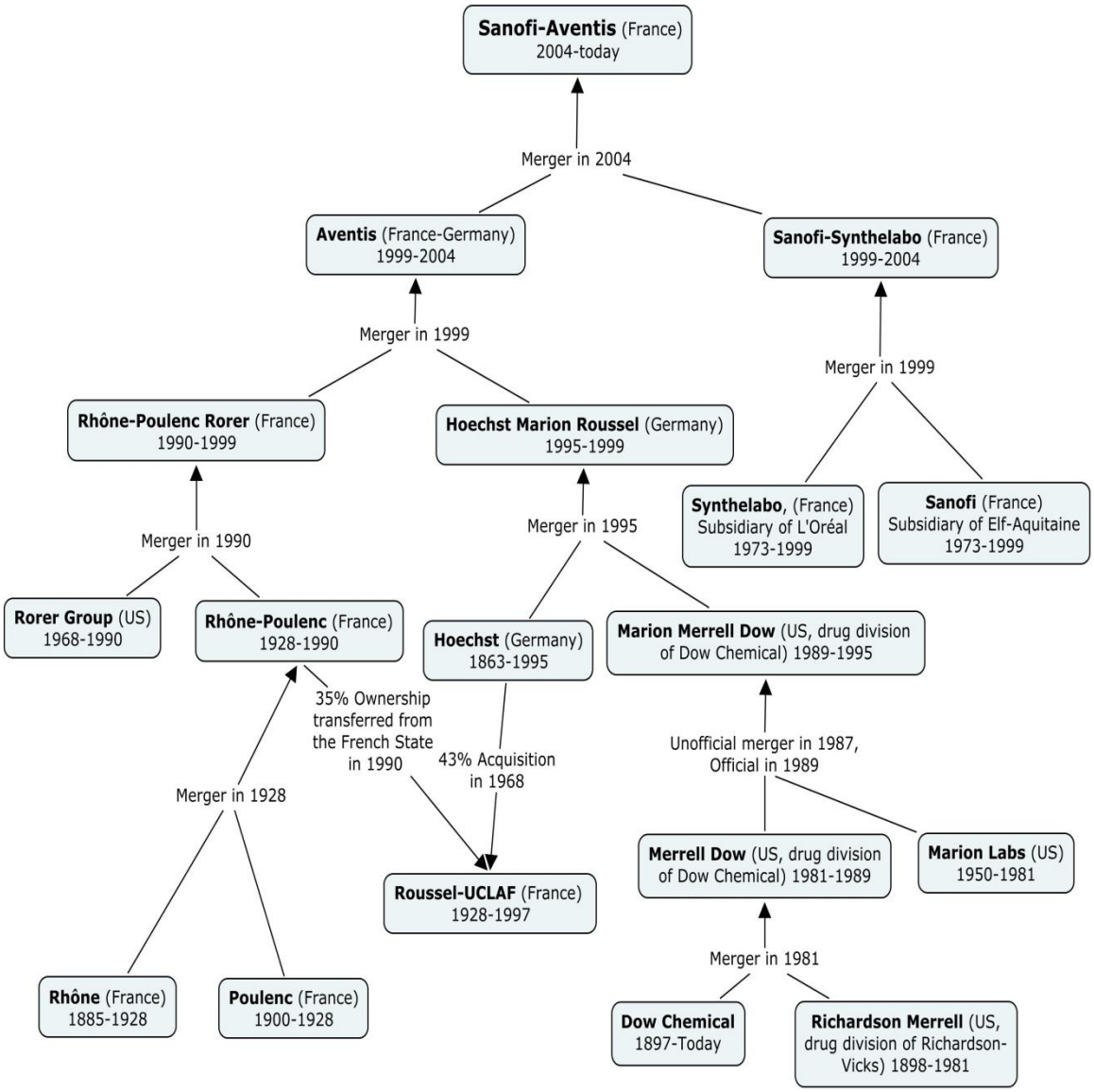
Figure 5.11: Novartis' Corporate Family Tree



Sources: Firms' corporate website, Chandler (2005), Derdak (various years) and Hoover & al. (various years).

In the case of France, the state remained involved in maintaining a French national champion. Sanofi was created in 1973 by the French government as a subdivision of the state-owned chemical and oil company Elf-Aquitaine. The latter was privatized in 1996, and when Sanofi became a target for M&As, the French government used its influence (and its remaining shares) to favor a "local solution" with the merger of Sanofi with another French firm, Synthélabo. When the remaining important French pharmaceutical firm Roussel-UCLAF was partly acquired by the German Hoechst in 1968, the French Socialist government thought of nationalizing the firm but, instead, obtained a partnership with Hoechst, providing the French government with 33% of the shares (in 1982 the state increased its interest to 40%). In 1982, the French government also nationalized Rhône-Poulenc, and transferred in 1990 its 35% remaining interest in Roussel-UCLAF to Rhône-Poulenc. Rhône-Poulenc was privatized in 1993, and merged with the German giant, Hoechst Marion Roussell, in 1999 to form Aventis, which was then half-French and half-German. The headquarters were even moved symbolically to Strasbourg, in Alsace. However, when the Swiss giant Novartis announced his intention to take over Aventis, the French government quickly intervened to arrive once again at a "local solution". The state encouraged Sanofi-Synthelabo to place a higher bid on Aventis and the merger took place in 2004, creating the French national champion, which is now the world's sixth most important pharmaceutical firm in terms of capitalization (Figure 5.12).

Figure 5.12: Sanofi-Aventis' Corporate Family Tree

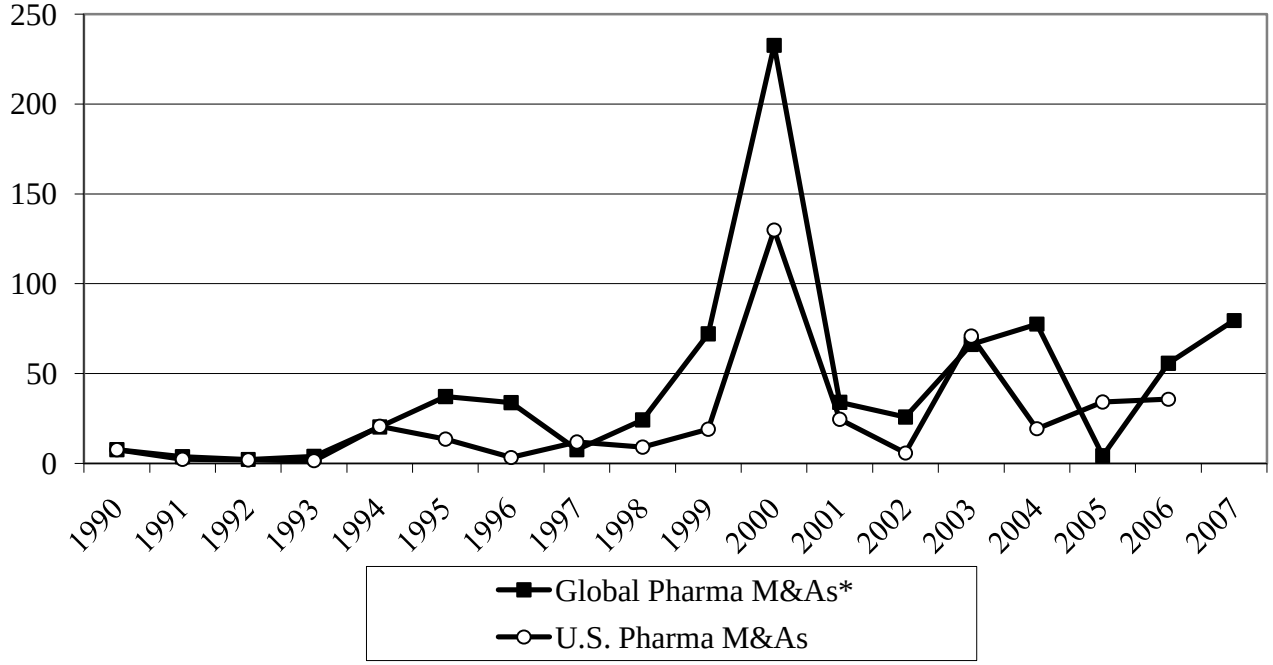


Sources: Firms' corporate website, Chandler (2005), Derdak (various years) and Hoover & al. (various years).

All these corporate family trees display an important acceleration in M&As since the beginning of the 1990s. The dominant Big Pharma firms intensified their concentration and

transformation into larger Behemoths. While it was explained at length how the U.S. restructuring of the pharmaceutical sector was central to this acceleration of M&As for American dominant firms, the corporate family trees allow us to observe that the same acceleration happened in other dominant countries, mostly in order to create national champions capable of competing with American giants, but also in order for foreign firms to develop capabilities, marketing and technology in the American market. In fact, numbers show that the evolution of global M&As did not differ significantly from the trends in the United States since 1990 (Figure 5.13).

Figure 5.13: M&As for U.S. and Global Pharmaceutical Firms, 1990-2007
(Billions $)



*: Only M&As of 25 millions $ or more are included in Global Pharma M&As, which explains why U.S. M&As are sometimes higher than Global M&As

Sources: Thomson Financials; Young (2008)

Analyzing the pharmaceutical sector in the 1980s through the framework of differential accumulation shows how central M&As have become to the accumulation regime put in place since the 1980s. Foreign dominant firms had to mimic their American counterparts, or else become easy prey themselves in the market for M&As. Contrary to the "New Economy" thesis, the obvious conclusion is that external growth was the prime path for increasing corporate dominance in pharmaceuticals from the beginning of the 1990s, not increased investment in new technologies or in R&D. Note that merger mania still seems far from over: Global M&A deals totaled $80 billions in 2007 (Figure 6.13), which is the best year in terms of M&As, after the amazing $230 billion peak of 2000. Still today, M&As are central to the accumulation regime in pharmaceuticals. In only the first seven months of 2008, a record number of 32 biotech firms have been acquired by larger firms for a total value of $72 billion (Economist 2008a). The financial crisis that rages since September 2008 has not slowed this process. On the contrary, it has accelerated the pace of M&As (Economist 2008b).

Interpreting the Merger Mania

What is the significance of such magnitude in M&As? The "New Economy" thesis and standard economics consider that growing profits must be the results of greater investments. The analysis provided in this chapter proves quite the contrary. Analyzing differential breadth shows the importance of external growth through M&As, as compared to internal growth through greenfield investments. Comparing dominant firms and smaller firms allows us to see that while smaller firms and public institutions were in fact engaging in R&D,

dominant firms focused on organizing new networks of agreements and M&As, in order to capture new technologies while developing mostly their marketing networks and capabilities. With the help of the state, increasing differential breadth stemmed from sectoral restructuring to facilitate acquisition and marketing of new compounds by Big Pharma. This does not mean that dominant firms ceased to finance in-house research or that "productive investments" totally disappeared from the realm of Big Pharma. In-house research still amounts to important numbers, but it is a secondary dimension of the on-going business model, which stresses much more importance of firms' capabilities to capture strategic externalities.

The analysis provided here does show an important trend that must be taken into consideration, since internal growth by greenfield investment, confined to the supporting nexus, remains a very elusive idea among Big Pharma firms. This trend is evident in firms' annual reports. In their accounting study based on the annual reports of ten firms included in Big Pharma, Lauzon and Hasbani (2006) identified an important "anomaly": the firms' astronomically large amount of cash reserves and liquidities. They show that in 2005, the ten most important pharmaceutical firms had accumulated reserve of cash and liquidities totaling more than twice all net investments in property and equipment between 1996 and 2005. With an average net return on equity of 28% for these firms during that period, and with 77% of all net benefits going to shareholders (through dividends and downsizing), remaining income is used less to finance new investments than to prepare for greater acquisitions. "Today's medicines finance tomorrow's miracles," says GlaxoSmithKline's advertising slogan. It would be more accurate to say that today's profits are used to acquire tomorrow's miracles, in a process that can only serve to consolidate Big Pharma's grip over the whole sector.

It is important to note that the analysis provided here on M&As is still incomplete. The magnitude of M&As also caused important concentration, which amplified monopolistic capacities of Big Pharma firms. As such, M&As directly contribute to the profit rate of Big Pharma firms. This dimension, however, can only be analyzed through the lens of differential depth, which will be the task of the next chapter.

6. DIFFERENTIAL DEPTH: THE INSTITUTIONAL FOUNDATIONS OF GREATER PROFITS

> The social responsibility of business is to increase its profits.
>
> -Milton Friedman (1970)

> The entrepreneur profits to the extent he has succeeded in serving the consumers better than other people have done.
>
> -Ludwig von Mises (1966)

> A businesslike control of the rate and volume of output is indispensable for keeping up a profitable market, and a profitable market is the first and unremitting condition of prosperity in any community whose industry is owned and managed by business men. And the ways and means of this necessary control of the output of industry are always and necessarily something in the nature of sabotage – something in the way of retardation, restriction, withdrawal, unemployment of plant and workmen – whereby production is kept short of productive capacity.
>
> -Thorstein Veblen (1919)

Differential accumulation is based on the accumulation of capitalist power as determined by capitalization and earning-capacities. Analyzing differential breadth revealed how important are M&As for this sector, and also how M&As are part of a general process that has restructured the sector in order to redefine the division of labor in pharmaceutical innovation to Big Pharma's benefit. While the importance of M&As is central to the ongoing accumulation regime in pharmaceuticals, it tells only one side of the story. Analyzing the evolution of differential accumulation in the pharmaceutical sector also requires the examination of the growing differential earning-capacity per unit of breadth. In other words, the *extent* of the firms' earning-capacity has to be coupled with the *intensity* of that earning-capacity. The focus must now shift from differential breadth to differential depth. Examining

differential depth allows one to explore the institutional foundations of the increasing profit rate in the pharmaceutical sector.

This chapter first identifies how to measure differential depth and presents the quantitative results for the pharmaceutical sector. These results are then used as benchmarks to assess the qualitative forces at work in this sector. Specifically, two main institutional differential earning-capacities are analyzed: 1) increased monopolistic power through concentration and 2) increased monopolistic power based on the extension of intellectual property rights. The chapter concludes by bringing together the results of the analysis in terms of breadth and depth, in order to draw a larger picture of the mechanisms at work in the accumulation regime in the pharmaceutical sector since the mid-1980s.

6.1 Differential Depth in the Pharmaceutical Sector

Depth refers to the intensity of profits. It is the difference between earnings and outlays. There are thus logically two ways to increase depth: by increasing earnings or by reducing costs. In order to increase earnings, a firm's main strategy is to sell more products, or to sell its products at higher prices. Certainly a firm can obtain some earnings from financial activities, but in the manufacturing sector, the bulk of earnings are normally revenues based on sales. The reduction in outlays can be the result of different cost-cutting strategies, for example decreasing tax rates, lowering wages, closing plants, laying-off employees, or lowering unit costs of products through innovation.

Differential accumulation is based on the amount of capitalist power held by firms, and not only on the size of firms. Accordingly, a larger firm in terms of breadth can have less capitalist power than a smaller firm with greater profit intensity. An example often cited is the comparison between Microsoft and General Motors (Rifkin 2000; Gagnon 2004; Nitzan 2004). In 2007, Microsoft, which embodies the contemporary knowledge-based firm, was third in the listing of the *FT Global 500*[63]: The firm had only $63 billion in assets and its revenues were only $51 billion while its market value (capitalization) was $273 billion (in March 2007) and its profits were $14 billion. At the opposite, General Motors, which has been the largest global firm most of the Twentieth Century, with huge investments in tangible capital and its large traditional industrial labor force, stacked up $182 billion in revenues in 2007 and owned $149 billion in assets. Its market value, however, was only $10.5 billion and it accumulated $39 billion in losses for that year. The depth of Microsoft is, to say the least, much more significant than General Motors, and the result is that Microsoft today, has much more capitalist power than does General Motors, even if the latter remains a larger firm in terms of breadth.

Thorstein Veblen did not theorize the breadth dimension of accumulation; he simply took it for granted that larger firms dominate the economy and then emphasized the architecture of business power behind this domination. According to Veblen, the bulk of capitalization of dominant firms is based on its intangible assets, which include franchises, government concessions, licenses, intellectual property rights, and goodwill. The latter is defined by Veblen as any monopolistic capacity that can increase the earning capacity of a business concern by controlling or restraining the supply of goods and services. Goodwill is

[63] The FT Global 500 lists the 500 most important global firms in terms of their market value.

the capacity to increase depth by increasing earnings without increasing production. It is a vested interest, which he defines as the capacity to get something for nothing. Specifically, monopolistic capacities and the control over the networks of distribution become central to increasing goodwill. Veblen even emphasized how much advertising has become an important dimension of goodwill creation as it establishes "differential monopolies resting on popular conviction" (Veblen 1996 [1904], 55). In contemporary accounting, however, goodwill has simply become the gap between the firm's market value and its book value when the firm is acquired by another, without any explanation of the causes for this gap. However, Hugh Hughes (1982), an accountant who studied the history of the concept of goodwill, shows that Veblen provided what remains the best theory to account for this concept in modern accounting.

Remember that, contrary to neoclassical economics, from a Veblenian perspective, the economic problem is not how things stabilize themselves in a "static state", but how they endlessly grow and change due to the cumulative causation between technology, the material milieu and institutions (habits of thought). Here, the analysis in terms of differential depth in the pharmaceutical sector becomes the examination of transformation in institutional power structures, particularly those that provide greater earning capacities (and smaller outlays) for dominant pharmaceutical firms within a perceived context of an emergent KBE.

Measuring Depth

Before analyzing the evolution of differential depth in the pharmaceutical sector, it is first necessary to consider the best way to measure the intensity of profits. At first sight, it

seems evident that depth should simply be measured as the rate of profit. What is less evident is how to measure the rate of profit.

The traditional way to measure the rate of profit is to use the internal rate of return, which is also defined as the return on investment (ROI). This measure is far from perfect, however, since it is based on the idea that investments relate to the creation or acquisition of productive assets and that we can thus measure the earning-capacity in relation to the productive capacity. This measure is thus still based on the productivity doctrine of capital, from which the institutional approach intends here to escape. Furthermore, an important bias exists with ROI in the case of pharmaceuticals due to existing accounting standards. In the United States, the accounting standards consider R&D and advertising to be expenditures instead of investments, meaning that the ROI is artificially inflated for that sector. Several studies (Clarkson 1977; Megna and Mueller 1991; Jensen 1993) show, for example, that it is baseless to compare ROI between pharmaceuticals and other sectors if we do not correct for expenditures in R&D. The studies suggest that the corrected ROI for pharmaceuticals should be between 18% and 36% lower than declared ROI. The differential evolution of ROI in pharmaceuticals could thus be the result of the evolution in the trends of R&D instead of the differential depth in relation to other sectors. In any case, ROI is not a particularly relevant standard and it is not accurate enough to measure differential accumulation.

Another typical standard is the return on assets (ROA). Since firm's breadth was defined earlier by the book value of its assets, even if it brings some problems with it, depth then normally should be considered to be the difference between earnings and outlays for each unit of asset. Thus, the rate of return on assets (ROA) would normally be the best way to measure depth. However, the difficulties for accurate ROI cloud also the capacity to

determine an accurate ROA since R&D and advertising expenditures are not directly considered assets. R&D expenditures can become assets, under the form of patents, and advertising expenditures can become assets in the form of trademarks, but there is no direct determination (and an important time-lag) between those expenditures and assets. ROA must then be discarded for the same reasons as for ROI.

Another standard, return on equity (ROE), also makes a poor standard for comparing firms from different sectors. ROE measures the rate of return on the ownership interest of the common stock owners. High ROE sectors are not necessarily more profitable than low ROE sectors since some sectors such as oil refineries can command a very large equity base, thus creating at the same time a large barrier to entry for that sector. The evolution of ROE can vary depending on corporate governance and financial structure (debt versus equity) with which the firm finances its activities. For example, in order to satisfy its shareholders, a firm can artificially increase its ROE by buying back its own shares since downsizing its equity increases the earning per share.

Nitzan and Bichler (2002b, 67) prefer to use the profit-per-employee ratio to measure depth. This standard is consistent with their measure of breadth based on the number of employees. Nevertheless, as identified in Chapter 5, the problems with measuring breadth in terms of employees remain. Specifically, it is difficult to compare profit per employee between a Wal-Mart cashier and a Pfizer researcher, and to make sense of the gap between the two in terms of a difference in the intensity of profits. One could argue that what matters is not a static comparison between sectors but the differential evolution of the profit ratio. In the case of the profit-per-employee standard, the problem remains since each firm, with its numerous departments, does not have a homogeneous workforce. For example, researchers

and sales reps are both central in the workforce of a dominant pharmaceutical firm. If the researchers are paid 30% more than sales reps, the development strategy adopted by the firm (i.e. more promotion and less research) will impact the evolution of profit-per-employee while it does not necessarily mean a change in the intensity of profit. For example, suppose that firm A develops a new strategy based on in-licensing compounds from firm B. Suppose firm A lays off its own researchers and uses the amount saved on wages to buy licenses from firm B. Suppose that, with the money gained from licenses, firm B does not need to manufacture its own drugs anymore, which it had been doing by outsourcing to a CMO. Suppose that with the money saved by terminating the outsourcing, firm B hires more researchers, and suppose that, in the end, firm A and firm B have the same income and outlays as before. Depth remains the same in both, but firm A now enjoys a much greater profit-per-employee, while firm B has seen an important decrease in its profit-per-employee. As explained in Chapter 5, the 1980s witnessed an important transformation in the division of labor in pharmaceuticals, and thus the profit-per-employee measure can be tricky since it might tend to overstate differential depth for dominant firms in that sector.

The standard that is favored here to measure differential accumulation is, instead, the return on revenue (ROR). ROR measures a corporation's profitability and is calculated as net income divided by revenue. ROR is the profitability measured as a ratio to sales. It has nothing to do with investments, and thus eliminates the bias in favor of knowledge-based firms in the way investments and assets are measured by excluding R&D. A static comparison in terms of ROR between sectors is baseless: some sectors with low value-added, such as retailing, have lower ROR than sectors with high value-added, which does not mean that they are less profit-intensive. Such a static comparison, however, is irrelevant to

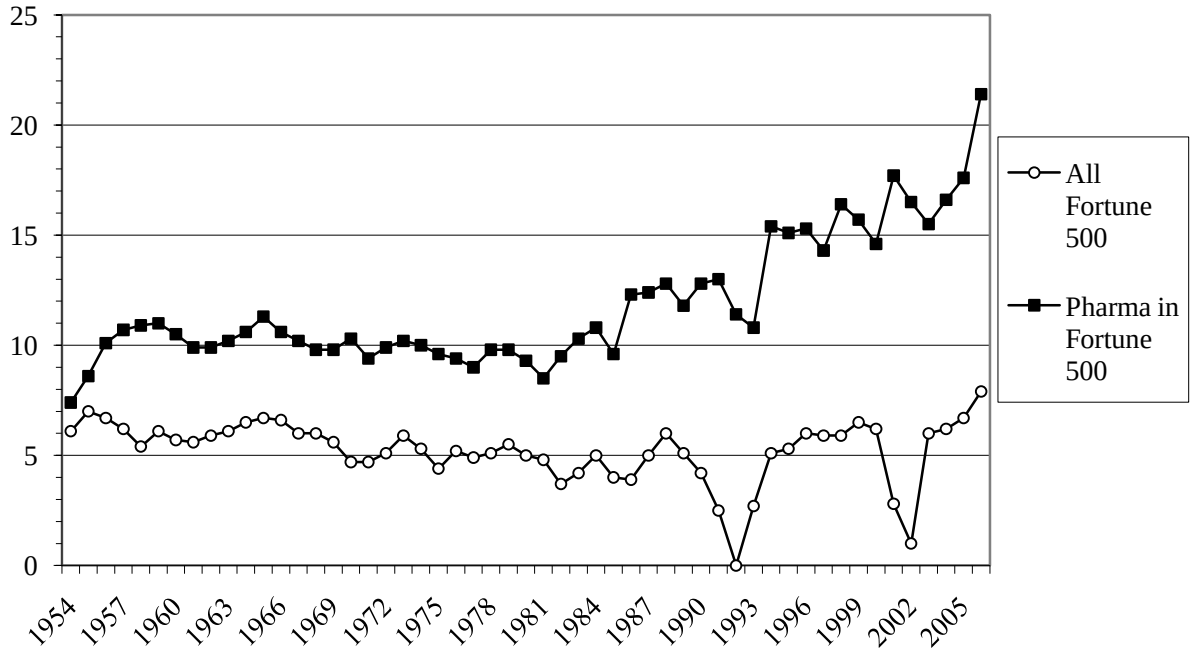
differential accumulation, since it must focus on the evolution of accumulation. ROR is particularly relevant in the case of pharmaceuticals since it measures the mark-up for each unit sold. Revenues in the pharmaceutical sector are almost entirely based on the selling of drugs. Some other factors, such as income from financial operations, cash payments to acquire other firms or the selling of discontinued operations, can have important sporadic impacts on revenues but, in the long run, the trends in ROR remain a good index of the evolution of mark-ups in a sector. The monopolistic capacities of pharmaceutical firms are observed by the important mark-up between prices and costs. This mark-up is central to many normative debates in the GPB because it is directly related to debates like access to essential medicines and the increasing health burden on public finances as compared to the profits of drug companies and their monopolistic capacities. An increase in ROR means an increase in the mark-up between cost and selling price per unit of drug: the greater the mark-up, the greater the monopolistic capacities behind it.

Another advantage for ROR is that, by focusing on the mark-up for each unit sold, it puts aside the dimension of global demand. For example, the aging of the population and the greater consumption of drugs surely help explaining the rising burden of healthcare on national expenditures and the rising share of pharmaceuticals in total healthcare expenditures. However, while those factors increase the quantity of drug units sold, they are not helpful to explain the evolution of the monopolistic capacities of drug firms, as observed through the evolution of mark-ups on each drug unit. It is the latter dimension that is of interest to differential depth.

Measuring Differential ROR

ROR is thus the standard used here to measure differential depth. By comparing the evolution of ROR for dominant pharmaceutical firms as compared to dominant firms in other sectors, it is possible to measure the differential depth for the pharmaceutical sector in historical perspective. For the same reasons as for the evolution of breadth, no historical ROR data are available for the GPB, but such data are available for American dominant firms through the Fortune 500 database. Using the same methods as for the differential accumulation of absolute profits (see Appendix A), ROR has been obtained by relating net profits to sales (Figure 6.1).

Figure 6.1: Differential ROR between Big Pharma and all Fortune 500 firms, 1954-2006



Source: Fortune Magazine

One can observe obvious trends in the evolution of differential ROR. First, there was a clear surge in differential profitability for pharmaceuticals from 1954 to 1958. Differential ROR remained particularly stable from 1958 until 1981, the date from which there is another surge in differential accumulation for pharmaceuticals until 1994. Differential ROR stabilized once again between 1995 and 2000 and became clearly positive for pharmaceuticals since 2000.

The positive surge in differential ROR in the 1950s matches with the emergence of a new business model in the GPB based on the vertical integration of R&D, manufacturing and marketing activities, as explained in Chapter 4. Instead of trying to obtain cheaper production processes for bulk manufacturing, dominant pharmaceutical firms began to focus on R&D and on the marketing of new drugs because, with their price inelasticity, patent-protected branded ethical drugs enjoyed greater monopolistic capacities and were thus much more profitable than OTC drugs or generics.

The second wave of positive differential accumulation began in 1981 and steadily rose until 2006, with only a short slowdown from 1995 to 2000. The emergence of what has been called the knowledge-based economy in the 1980s is clearly linked here to an increase in differential ROR for pharmaceutical firms. By understanding the reasons behind this increase in differential ROR, it is possible to better understand the capitalist dynamics involved in the increase of mark-ups in the GPB.

Importantly, the analytical tools used to examine differential accumulation, such as differential ROR, do not render a better understanding of the evolution of global demand due to the aging of the population or the medicalization of human conditions (Moynihan and

Cassels 2005). The tax issue was also found to have little impact on differential profits even if some tax cuts were put in place specifically in order to promote R&D in pharmaceuticals, such as under the Economic Recovery Tax Act of 1981 and the Orphan Drug Act of 1984. As explained in Chapter 3, those tax cuts did not reduce outlays by pharmaceutical firms but, instead, increased spending in R&D in relation to sales in the 1980s[64]. The tax issue is thus not part of the explanation of the growing differential ROR. However, the rising expenditures in R&D can be a factor, especially when we consider the extension of intellectual property rights over innovation in the 1980s.

Based on the research results already obtained, two reasons were found to be crucial in the rising discrepancy in ROR since 1981 between pharmaceuticals and other sectors. The first is the rising monopolistic capacity of pharmaceutical firms because of industrial concentration and increased cooperation. The second reason that needs exploration is the extension of intellectual property rights based on economic policies designed to return America to its status as world technological leader. Intellectual property rights are temporary monopoly rights, and their extension in the pharmaceutical sector translates directly into the price increase of drugs, and the increase of mark-ups. The next two sections explore at length these two factors.

[64] An issue that could be of interest, however, would be the ethical debate about the sources of R&D funding in health research. By compiling all expenditures in health research, one can find out that, if we include public funds through taxpayers subsidies, 60% of global expenditures in health research comes from public fund (Global Forum for Health Research 2006, 43) while most innovation are appropriated by private interests. This important normative debate would bring us far outside the main concerns of this dissertation and cannot be examined here at length.

6.2 Combinations and Monopolistic Power

Chapter 5 revealed how central M&As were to the ongoing accumulation regime in order for Big Pharma to benefit from a new division of labor in pharmaceutical innovation. The growth in the size of firms can also have an important impact on the degree of monopoly and, consequently, on monopolistic capacities to increase prices and markups. While a competitive market imposes a competition in terms of prices, reducing markups accordingly, consolidation and concentration do not only increase breadth, but also depth. For example, Immanuel Wallerstein (2002) explains that in a perfectly competitive market, no seller would make a substantial profit since a buyer could go from one seller to the other until he obtained the product at cost. This situation would be a nightmare for capitalists, and Wallerstein therefore considers that the first principle in a capitalist economy should be that the market is the enemy of profits, and that monopolistic capacities are thus vital for capitalist accumulation.

From a Veblenian point of view, the institutional structures of the corporate business sector with the formation of corporations, pools, trusts and holdings, were created mostly to prevent overproduction that would result in falling profits (Roy 1997). In fact, the oligopolistic market structure emerged in order to reduce price competition dramatically (Stanfield and Carroll 1997, 842; Baskoy 2003, 1128). Or, as Dillard puts it (1987, 1627), following Veblen: “The general rule of business is to charge what the traffic will bear. Monopolistic pricing becomes pervasive in the era of large-scale enterprises”. It is necessary here to measure and examine at length the oligopolistic structure and the corporate

concentration at work in Big Pharma. To put it bluntly, the purpose of this section is to show how much of a global cartel the GPB has become.

Measuring Corporate Concentration

Analyzing the oligopolistic structure of the GPB requires measuring corporate concentration. It is important here not only to measure monopolistic capacities based on market shares but also the intensity of cooperation among Big Pharma. It was already demonstrated that the sixteen firms which comprise Big Pharma have captured almost two thirds of the global pharmaceutical market (figure 3.3). This domination by a handful of firms over a whole sector is not unusual. In automobiles, aircrafts or cigarettes, it is well known that even fewer firms control these sectors. One may contend that concentration is not a problem in pharmaceuticals, since if 16 firms control this market, that is in fact a lot of firms, and so market competition between them will ensure that no firm will be able to benefit from its partial control of the knowledge structure. This analysis seems correct if we compare the concentration ratio of the four largest firms (CR_4)[65] of pharmaceuticals with that of other business sectors (table 6.1).

[65] The CR_4 is a widely used index to measure business concentration by calculating the market share controlled by the 4 largest firms in each industrial sector. The market share can be evaluated in terms of sales or in terms of value added. A CR_4 of over 50% is generally considered a tight oligopoly; CR_4 between 25% and 50% is generally considered a loose oligopoly. A CR_4 under 25% means no oligopoly at all.

Table 6.1: Concentration of Selected Industries in the United States in 2002
(CR_4 Based on Value Added)

Manufacturing Sector	NAICS	Number of firms	CR_4 Value Added
Cigarette	312221	15	95.3%
Automobile	336111	164	87.3%
Electronic Computer	334111	465	80.6%
Aircraft Mfg	336411	184	80.2%
Soap and detergent	325611	699	63.1%
Sugar Mfg	31131	52	52.8%
Petroleum Refineries	32411	88	46.7%
Pharma Preparation	325412	731	34.9%
Paper	322	3537	30.4%
Apparel Mills	315	12 550	18.4%

Source: U.S. Census Bureau (2006)

Business lobbies often quote this type of concentration ratio to show that the pharmaceutical sector is in fact a very competitive business. Independent analysts sometimes use the same logic (Redwood 1987, 80-87). The portrait is inaccurate, however, due to inelastic demands for pharmaceutical products according to their therapeutic class. With automobiles, one can always substitute his compact car for a SUV, whereas in pharmaceuticals, one cannot substitute his ulcer drug for an allergy drug. The heterogeneous nature of drug products results in different therapeutic sub-markets with very low cross-elasticity of demand. The firms' market power as measured by the CR_4 should thus be measured according to each therapeutic class. As McIntyre (1999, 54) notes, it is within these

submarkets that the true nature of the pharmaceutical business emerges. Recent data based on the concentration of sales for each firm by type of drug show how concentrated this business has become (table 6.2). Note that the table does not categorize drugs according to official ATC classification. Also, the proposed classification does not necessarily define relevant markets. For example, Cipro, produced by Bayer, is considered to be the only reliable antibiotic to effectively treat cases of anthrax[66]. With a CR_4 on sales between 51 and 100 in every category, table 6.2 clearly shows that a tight oligopoly exists in every drug class.

[66] The monopoly power of the German firm was thus greatly felt during the anthrax scare in 2001 in the United States, where the American and Canadian governments threatened to use compulsory licensing of Cipro for reasons of national security.

Table 6.2: Market Shares of 4 Leading Firms by Drug Class, 2007

Drug Class	Firms and Market Shares (%)				CR_4 (%)	Total Sales per Drug Class ($ Billion)
Alzheimer's Disease	Pfizer (47)	Novartis (21)	Forest (21)	J&J (11)	100	3.1
Arthritis	J&J (19)	Amgen (17)	Abbott (16)	Pfizer (15)	67	19
Cardiology	Pfizer (25)	Sanofi-A. (13)	Merck (10)	Novartis (10)	58	73
Central Nervous System	Eli Lilly (20)	J&J (15)	AstraZeneca (13)	GSK (12)	60	37
Diabetes	Novo Nordisk (27)	Sanofi-A. (19)	Eli Lilly (14)	Takeda (14)	74	21
Epilepsy	J&J (44)	Pfizer (20)	GSK (19)	Abbott (12)	95	11.4
Gastrointestinal/ Ulcer	AstraZeneca (50)	Wyeth (16)	J&J (15)	Abbott / Takeda (6)	87	13
Head Trauma/ Spinal Cord Injury / Stroke	Roche (80)	Bayer (20)	------	------	100	0.13
Infectious Disease	GSK (25)	Merck (10)	Wyeth (8)	Roche (8)	51	49
Multiple Sclerosis	Biogen / Elan (32)	Sanofi-A./ Teva (25)	Merck (24)	Bayer (20)	100	7

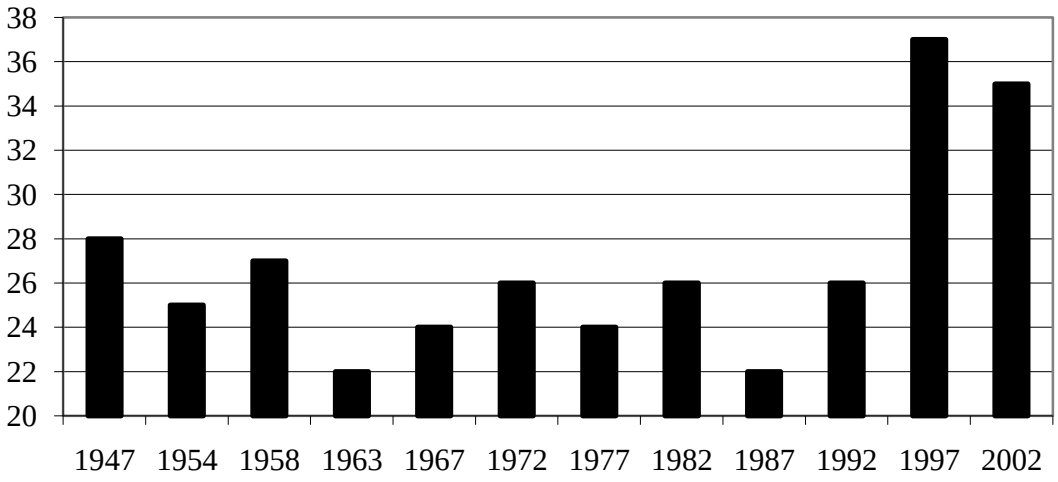
Drug Class	Firms and Market Shares (%)				CR_4 (%)	Total Sales per Drug Class ($ Billion)
Obesity	Roche / GSK (66)	Abbott (16)	Sanofi-A. (6)	------	100	1.1
Oncology/ Hematology	Roche (27)	Amgen (17)	Novartis (11)	Sanofi-A. (8)	63	63
Ophtalmology	Pfizer (31)	Allergan (18)	Merck (16)	Novartis (11)	76	5.5
Orphan Diseases	Genzyme (76)	Shire (14)	BioMarin (6)	Alexion (3)	99	2.3
Osteoporosis/ Hormone Replacement	Eli Lilly (35)	Merck (33)	Wyeth (11)	Novartis (3)	82	9
Pain Management	J&J (29)	Purdue (26)	Endo (26)	Cephalon (12)	93	4.2
Respiratory	GSK (36)	Merck (15)	AstraZeneca (13)	Schering-P. (10)	74	28
Sexual Dysfunction	Pfizer (29)	Eli Lilly (19)	Bayer/GSK/ Schering-P. (6)	-------	54	6.1
Sleep Disorder	Sanofi-A. (72)	Sepracor (21)	Takeda (3)	------	96	3
Urinary Incontinence	Pfizer (60)	Astellas/ GSK (16)	Novartis (9)	J&J (3)	88	2

Source: Cowen and Co. (2008), Investext

Table 6.2 tells us nothing, however, about the evolution of corporate concentration over time. The best measure of the historical evolution of concentration in pharmaceuticals is provided by the U.S. Census Bureau, which has analyzed concentration ratios at every census since 1947. While the U.S. Census does not provide historical data of the evolution of concentration ratios by therapeutic classes, the evolution of the ratio for all pharmaceutical preparation manufacturing can serve as a proxy to understand the on-going systemic evolution (figure 6.2).

Figure 6.2: Historical Evolution of the CR_4 in the U.S. Pharmaceutical Sector

(From 1947 to 2002; CR_4 on value added)



Source: U.S. Census Bureau (Concentration Ratio, various years)

This historical evolution shows a sharp increase in concentration in the 1990s, which is consistent with the data on M&As. Concentration decreased in the 1980s with the emergence

of biotech firms on the U.S. market, but the 1990s witnessed an important consolidation of the industry, bringing the CR_4 from 22% in 1987 to 35% in 2002. It seems likely that the same trend occurred approximately in the same way in each therapeutic class. One can presume that the tightening of the oligopoly was more important in pharmaceuticals than in other sectors since Chapter 5 showed that the trend in M&As in the 1990s was more important for dominant pharmaceutical firms than in other sectors. Measuring monopolistic capacities based only on concentration ratios remains, however, a very limited approach. Such measure can only give a rough idea of how tight the oligopoly controlling the sector is, but the size of the oligopoly provides few indications about the cartel dynamics at work between the firms of this oligopoly. Such dynamics are central to the power structure at work in the control of business.

Cartels and Cooperation Agreements

Cartels abounded in the 1930s, but declined after the Second World War. The U.S. Department of Justice discovered only a few cases of international price-fixing agreements from 1955 to 1985, including a case of price-fixing in antibiotics, and none between 1985 and 1994. Since 1994, a cartel revival was observable since 20 international cartels were uncovered. Two of those cartels were found in pharmaceutical products: one in lysine (an essential amino acid), which managed to increase world prices by 70% on that substance, and another in vitamins (Connor 2008). In fact, it was the discovery of the cartel in lysine that brought antitrust authorities to open investigations in other sectors. The investigations of the lysine cartel revealed how easy it was to organize a price-fixing agreement, and created a public uproar by exposing the sharp disdain such firms had for their customers. For example,

in a FBI tape of one session of the cartel, ADM's president and lysine cartel leader, James Randall, explains: "We have a saying in our company: Our competitors are our friends, our customers are the enemy."

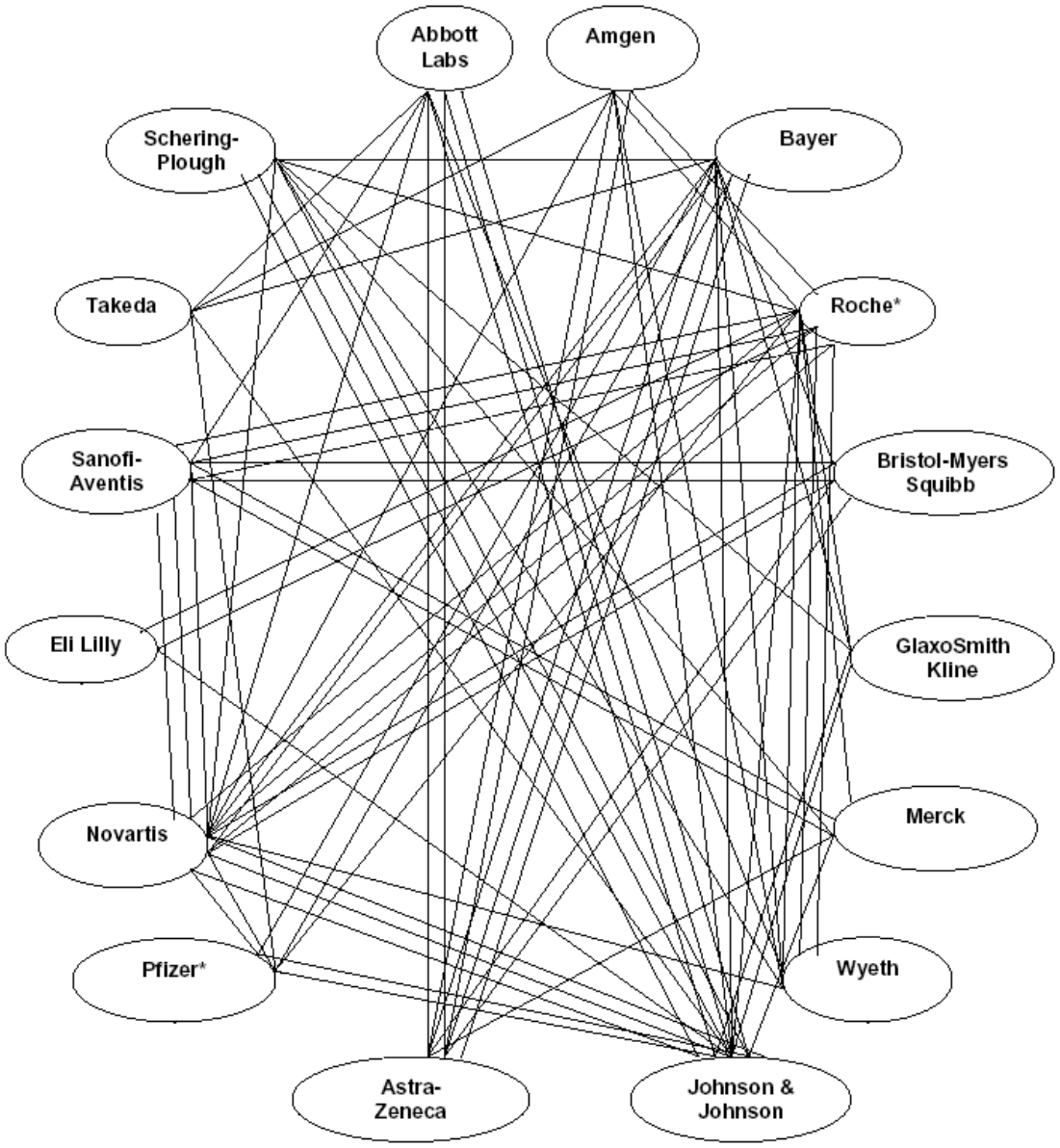
Such "traditional" price-fixing agreements remain officially illegal according to competition policies in most industrialized countries: they are normally prosecuted by law, and should not be considered central within the structure of Big Pharma. It has already been explained how intellectual property rights managed to replace plain cartel agreements in the 1920s and 1930s. As in the case of DuPont, cartel agreements often took the form of cooperation agreements, normally based not only on patent pooling and cross-licensing agreements, but also on joint ventures, technology transfer, R&D or marketing agreements. These latter types of cooperation agreements, which abound today, can bring the same results in their ability to manipulate prices, divide market shares, control research agenda, reduce costs and restrain competition.

Chapter 5 analyzed the restructuring in the division of labor in pharmaceutical innovation and the externalization of R&D to smaller firms in the 1980s. Big Pharma maintained its control over the sector thanks not only to its important financial resources that allowed it to buy back any promising compound, but also by creating important networks of agreements with biotech firms and universities. To illustrate the surge of cooperation agreements in the 1980s, Gambardella (1995, 63-75) used the database Bioscan, and listed all on-going cooperation agreements in 1992 for four firms: Ciba-Geigy (now Novartis), Hoffmann La Roche (now Roche), Merck and Pfizer. Using the same database today allows one to compare the evolution of the importance of cooperation agreements since 1992, but the comparison is limited since Roche and Pfizer do not declare their cooperation agreements

anymore. Ciba-Geigy (later Novartis) declared 25 on-going cooperation agreements in 1992 and Novartis declared 39 such agreements in 2008. Merck doubled its cooperation agreements from 33 in 1992 to 65 in 2008. Another firm, AstraZeneca, declared more than 1700 collaborations and agreements in 2008. In order to illustrate the nature of such cooperation, the details of the cooperation agreements are included in the Appendix for Merck (Appendix B), and for AstraZeneca (Appendix C).

Numbers obtained through the Bioscan database thus suggest that the level of cooperation has increased even more since 1992. While the surge in cooperation agreements since the 1980s could be viewed as the result of the restructuring of the division of labor in pharmaceutical innovation between Big Pharma and its supporting nexus, as Gambardella (1995) emphasizes, more and more cooperation agreements in the 1990s were made between and among dominant firms. The relaxation of antitrust regulations brought back a pseudo-cartel structure in the same way that it existed in the 1930s (see Chapter 4). For example, using the Bioscan database (as updated with the daily Bioworld publication), it is possible to list declared cooperation agreements by dominant firms (or subsidiaries) with other dominant firms (or subsidiaries). By drawing a line for each agreement, figure 6.3 shows that the web of cooperation among Big Pharma firms in 2008 gets, to say the least, particularly thick (see Appendix D for details about the cooperation agreements).

Figure 6.3: On-Going Cooperation Agreements Among Big Pharma
(May 2008)



*****: Pfizer and Roche did not individually declare their cooperation agreements. There is thus the possibility that the number of cooperation agreements is understated for those two firms, particularly the agreements between them.

Sources: Bioscan and Bioworld

With 82 declared cooperation agreements among the 16 firms embodying Big Pharma, this means that each dominant firm has on average more than ten cooperation agreements with other dominant firms. Some firms tend to cooperate more than others: only three agreements were listed for Eli Lilly, while 19 were listed for Novartis and J&J. Nevertheless, in this cooperation web, there is no visible central knot, and we find ourselves clearly facing a network of cooperation, and not a pyramidal structure with a central decision-making process. Market competition in the pharmaceutical sector here becomes an elusive concept when compared to the reality of organized systematic cooperation. While there is no cartel agreement in the legal sense of the word, we find ourselves confronted with the multiplication of quasi-cartel agreements, which results in the same consequence: increased monopolistic capacities.

For the purpose of this dissertation, it is clear that monopolistic capacities are being developed in the pharmaceutical sector, including greater combination through mergers and acquisitions, and greater collaboration based on the multiplication of cooperation agreements among and between Big Pharma firms. Because of the lack of data, it is not possible to compare the details of the intensification of corporate concentration and collaboration with the evolution of differential ROR. Nevertheless, it is possible to conclude that the overall augmentation in corporate concentration and cooperation caused, at least partially, an overall increase in differential ROR. However, business concentration and cooperation is not the only factor behind the growing ROR of Big Pharma. The impact of regulatory transformations, particularly in terms of the extension of intellectual property rights also needs to be considered.

6.3 The New Regime of Intellectual Property: Made in USA

Intellectual property rights (IPR) are an important form of intangible assets, in the Veblenian sense, since they provide their owner legal monopolies. From the beginning of the 1980s, we observed an important extension of monopoly power provided by IPR, and this extension had its roots in an American strategy to recapture global technological leadership, in pharmaceutical and other sectors. After explaining the institutional nature of IPR, this section argues that the increasing earning capacity and positive differential depth in the GPB is, in part, the result of a U.S. strategy to transform the American and global knowledge structure in order to consolidate the position of U.S. dominant pharmaceutical firms by allowing them greater control and power over global technological capacities. The rest of this chapter explores the transformation of the IPR regime in the United States in the 1980s, and then analyzes the transformation of the global IPR regime championed by the United States, as well as the consequences of those transformations in the pharmaceutical sector in terms of monopolistic capacities and therapeutic innovation.

The Nature of IPR

The existence of intellectual property rights (IPR) is generally justified as a palliative to the inherent incapacity of the market to reward innovation, be it industrial, intellectual, artistic or commercial. It is considered that, with the presence of increasing returns to scale and output priced at marginal cost, R&D firms could not survive as price takers since they would not cover the cost of developing the technological innovation that gave the firms their

increasing returns-to-scale "production function" (Fulton 1997). The nature of IPR is not without contradictions; it seeks to compensate for the deficiencies of the market by granting "legal monopoly rights" over ideas, knowledge and techniques; it thus compensates market deficiencies by distorting the market even more. Stronger IPR are normally considered to offer a faster pace for technological progress, which creates more wealth for the community. Nevertheless, once the innovation exists, the logic is inverted: Stronger IPR normally mean greater net loss for the general welfare of the community since innovations are less diffused (the cost to access the protected innovations being greater). The absence of IPR would then mean a greater technological diffusion and maximal general welfare according to the state of existing technologies, but it would also mean less innovation to diffuse. As the economist Joan Robinson explains: "The justification of the patent system is that by slowing down the diffusion of technical progress it ensures that there will be more progress to diffuse" (quoted in Hettinger 1989, 48). PhRMA uses the same type of explanation to justify greater IPR in pharmaceuticals (PhRMA 1998, 79): "Without patent protection, it is highly unlikely that a company would be rewarded for its invention – or, more importantly, that patients would receive many new medicines". In standard textbooks, the dilemma over IPR is thus as follows: How can we ensure the greatest technological development (with stronger IPR) while maximizing technological diffusion (with weaker IPR). The duration of patents must be determined in a way that maximizes the social welfare of the community. IPR are here justified from a utilitarian perspective as the equilibrium between production and diffusion in order to ensure the greater common good.

From an institutionalist perspective, IPR must be considered from a different angle. Property must be understood not as a natural right of an individual to the things he owns (see

Vachet 1988; MacPherson 1962), but as a judicial regime distributing property rights among individuals, rights to exclude others from the use of different objects. Following Thorstein Veblen and John R. Commons, Morris Cohen (1927) developed the idea that one's *dominium* over his objects is also an *imperium*[67] over human beings since it is a power to exclude others from the objects owned. Private property should thus be considered as private power over others (Cohen 1927, 12).

Property over physical objects is normally embedded in clear-cut physical frontiers, which limits the extent of power obtained through the property of physical objects. Property rights over abstract intangible objects, like IPR, have no clear-cut frontiers and can provide power over complete categories of physical objects, the delineation of which can evolve over time (Drahos 1996, 155). Many patents seem insignificant,[68] but their accumulation can lead to the acquisition of great power over others. The frontier of those abstract objects are constantly being repositioned and firms can use patents over abstract objects that might seem futile at first to claim important compensation from human activities that often have little relation with the abstract object.[69] Property rights over abstract objects can thus provide great private power over important resources of the community by creating important forms of

[67] Roman law discriminated between *dominium*, the rule over things by the individual, and *imperium*, the rule over all individuals by the prince.

[68] For example, in the United States we can find patents on a peanut-butter-and-jelly sandwich (#6,004,596), on a method of using a backyard swing (#6,368,227) or a method of combing hair over a bald spot (#4,022,227) (Bessen and Meurer 2008, 2).

[69] For example, a firm holds patents that it claims cover current technologies that allow people to make internet phone calls, and all internet phone calls should thus get them some royalties. IBM patented the generation of paragraphs or footnotes on a computer, which gives them an earning-capacity from all academic texts produced on computers (Economist 2000). Another firm pursues colleges for royalties on distance-learning programs with a patent claim on streaming video on the internet (Sewell 2007); Accompany.com patented the capacity of group-buying on the internet, Amazon.com patented the "one-click buying" and Walker Digital patented the capacity to offer advice online (Economist 2000). In biotechnology, upstream patents over genes provide earning-capacity over all subsequent health research in which the gene is involved.

dependency. As Drahos (1996, 158) explains in his book about the philosophy of intellectual property rights:

> Once the law creates abstract objects in relation to resources like genes, seeds, chemical compounds or forms of medical treatment it opens the way to the private ownership of resources upon which there is some level of collective dependence. For the economist, creating abstract objects in these kinds of resources is justifiable if there are real dynamic efficiency gains to be had that outweigh the costs of such rights. But there is a broader consequence to consider here, one that is harder to measure in terms of some economic metric, and this is the potential effect of abstract objects upon the distribution of power within a given social system.

Because of the abstract nature of the objects of their *dominium*, IPR can bring extraordinary private power if they are not entrenched in the idea that we need to find the proper equilibrium between innovation and diffusion. If it is not the case, private power can create collective dependencies over essential aspects of human life like food, education, culture, health or human reproduction. Of course, the usual forms of property can also create collective dependencies. For example, Karl Marx explained at length how the private ownership of the means of production maintained the domination of the capitalist class over workers while respecting the liberal credo in favor of liberty, equality and property (Marx 1887, Chapter 6). IPR, however, go further since they can restrain production even from those who are actually the owners of their means of production (for example by restraining the production of generics). IPR can stipulate the conditions and limits of the use of an object in the private sphere, as in the case of the use of seeds, information or cultural goods. With IPR, we now find new forms of personal dependency overlaying the existing ones emanating from the usual forms of property. Indeed, another person might be able to decide the conditions with which I may use my own objects in my private sphere if that person owns a

right over the abstract object, the concept behind the physical object I own. That person can thus own a coercive power, or 'threat power' (Drahos 1996, 160), over my own activity, over my own *dominium*.

The problem has become acute in recent years since the judicial construction of the IPR regime has been mostly influenced by corporate oligopolies. Private interests have thus appropriated extraordinary powers through the accumulation of IPR and developed collective dependencies to increase their earning-capacity. For example, Friedrich Hayek (1944, Chap.3) distinguishes individualism from collectivism by considering how central competition is in the organization of social life. For Hayek, the great merit of competition is that it limits the extent of the power that an individual can possess over the community, while the danger of collectivism is that all powers are centralized in the hands of planners, creating an important dependency of the community towards planners. It is contended here that the extension of IPR acted just like Hayek's central planning, by concentrating power in the hands of a corporate elite. As Drahos explains (1996, 163):

> States that enact property forms that enable private sovereigns to harness enormous threat power embark on a dangerous strategy, for they increase the capacity of those private sovereigns to discipline markets and to plan against competition. Private sovereigns, like their collectivist counterparts, are likely to plan against competition rather than for it.

Such concentration of power through IPR was central to the increase of differential depth and the growing differential ROR for the U.S. pharmaceutical sector in the 1980s.

Commodification of Public and Academic Research

By the end of the 1970s, there was a prevailing perception that the U.S. was beginning to lose the race for technological supremacy (see Chapter 4). Developing countries were understood to be "stealing" America's ideas by implementing unfair trade practices. Because of this perceived decline in U.S. competitiveness, a series of legislative acts were put in place to improve the U.S. position in high technology sectors. A technological "fix" had to be found for U.S. corporations and, in 1980, the new Republican Administration led by President Reagan, embarked on multiple state interventions to lend a hand to high technology sectors. The first steps were to improve cooperation between public and private sectors by encouraging universities and public institutions to patent their findings in order to facilitate the transfer of technology to the private sector.

As is illustrated by Tyson (1996), one of the principal causes of the perceived loss of competitiveness by the U.S. innovation system was its over-emphasis on basic research, and the inability to translate this research into concrete results for firms in a speedy and efficient manner. Public investment in R&D was not believed to be effective enough to maintain American leadership in terms of global competitiveness. Those perceived deficiencies in R&D public policy became preeminent problems for federal authorities. As Coriat and Orsi (2002, 1493) explain:

> This point of view, which quickly began to dominate decision-making circles, gave birth to a series of studies and works that were often sponsored by government authorities and which were intended to modify the general operational framework of the different actors involved in innovation activities. Finally, the changes that took place lead to the building of a series of new "institutional complementarities" [...] Within 20 years, these would totally change the dynamics of the US [National Innovation System].

For the pharmaceutical sector, the commodification of academic and public research was a major technological "fix", since it provided incentives to articulate public and academic research to the needs of the industry, opening the door to more corporate influence on campuses and in public institutions. The corporate influence over academic institutions had been established for a long time (see for example Veblen 1918), but those new policies brought corporate influence to new heights. As Krimsky explains (2004, 5), in the 1980s, federal research policy became, for the first time since World War II, part of a new agenda to reinvigorate American economy by creating closer linkages between universities and industry. The policy change came with the 1980 Stevenson-Wydler Technology Transfer Act that gave guidance to federal agencies on increasing technology transfer and mandated them to set up Offices of Research and Technology Applications. The law stressed the importance of transferring public research to private firms. This first law was consolidated later the same year with the 1980 Patent and Trademark Amendments Act, better known as the Bayh-Dole Act, which allowed the patenting of inventions made through public funds. The Bayh-Dole Act, in fact, encouraged universities and public institutions to organize their research in such a way as to obtain patents in order to make the inventions more easily marketable for firms through licensing. Initially, however, the act was relatively limited, since it gave title to inventions made with federal funds only to universities, small business and non-profit organizations. Moreover, only small firms could obtain licenses from those inventions. Pressure from consumer groups and the remaining strength of Antitrust divisions explain this state of affairs (Malissard et al. 2003). It was only a very discrete memorandum by President Reagan in 1983 that generalized the imperatives of the Bayh-Dole Act to dominant firms.

Partnerships between the industry and academic institutions multiplied, accelerating the transfer of academic research and its commercialization. Such partnerships began to mushroom in the biotechnology sector. By 1984, industry support for academic research in biotechnology amounted to $120 million, which was about 42% of all industry-supported university research (Krimsky 2004, 32). A summary statement of a workshop on intellectual property rights held by the National Research Council (1996, 1) highlights the impact of those transformations in public policies:

> University patenting steadily increased from 1965 to about 1980, when there was a sharp increase in patenting that has continued into the 1990s. From 1965 to 1992, university patents increased by a factor of over 15 from 96 to 1500, whereas total patents increased by only about 50 percent. By the year 2000, universities had been awarded over 3200 patents. The greatest portion of the increase in university patenting has been in biomedical sciences, and many university patents cover inventions that are useful primarily for scientific research.

Those transformations, however, not only caused an increase in patenting, but also, as explained in Chapter 5, accelerated the division of labor between dominant firms with important marketing capabilities and smaller units concentrating on R&D, now including universities and public research institutions. A symptom of this acceleration can be observed in the upsurge of cooperation agreements between dominant U.S. pharmaceutical firms and public research institutions beginning in 1983 (Table 6.3). Those networks of agreements are presented in more detail by Gambardella (1995).

Table 6.3: Cooperation Agreements Between U.S. Dominant Pharmaceutical Firms and Federally Funded U.S. Research Institutions, 1984-1991

U.S. Big Pharma	Agreements with U.S. Research Institutions
Abbott Labs	- National Institute of Health - University of Chicago
American Home Products (now part of Wyeth)	- Columbia University - Stanford University - National Technical Information Service
Bristol-Myers Squibb	- University of Alabama - MIT - National Technical Information Service - Yale University - US Dept. of Health and Human Services - National Cancer Institute - Oxford University
Johnson and Johnson	- Columbia University - MIT - Scripps Clinic
Eli Lilly	- Columbia University - Scripps Clinic - MIT
Merck	- Duke University - Purdue University - Massachusetts General Hospital
Monsanto (Biopharmaceutical division now part of Pfizer)	-California Institute of Technology -Columbia University -Washington University
Schering-Plough	-Massachusetts General Hospital -Oregon State University -Pennsylvania State University -Scripps Clinic
SmithKline Beecham (now part of GlaxoSmithKline)	-Ohio State University -Walter Reed Army Medical Center -National Institute of Health -Stanford University -University of Cambridge -John Hopkins University -Washington Research Foundation
Sterling Drugs (now part of Sanofi-Aventis)	-Purdue University -Memorial Sloan-Kettering and Columbia University
Upjohn (now part of Pfizer)	-California Institute of Technology -US Department of Commerce -Battelle Memorial Institute -University of Kansas -Stanford University -National Cancer Institute

Sources: Bioscan; Gambardella (1995)

One should note that this modification of the U.S. innovation regime would soon become the model proposed by OECD to other countries in order to increase national competitiveness. The multiplication of Technology Transfer Offices in the universities of industrialized countries is directly linked to the American model (Malissard et al. 2003; Milot 2005).

From Encouragement to Enablement

Improving private-public partnerships was not the only issue, however. Due to antitrust sentiment that prevailed until the end of the 1970s, domestic patents were not easily enforced in the U.S., and this was a problem for the pharmaceutical sector, since it relied so much on this device. In fact, would-be domestic competitors had little to fear from infringing on patents. For example, when Eastman Kodak decided to develop an instant camera to compete with Polaroid, it issued an internal note to its employees in 1976 that stated: "Development should not be constrained by what an individual feels is potential patent infringement" (as quoted in May and Sell 2006, 140). May and Sell (2006, 140) consider that such behavior was the result of the lax enforcement of IPR by the state:

> The patenting practices that had helped underpin corporate power earlier in the century were constrained through a lack of governmental support. The dependence of intellectual property on legal (policy-related) action was its fatal weakness as a strategy for controlling markets, when such support was withdrawn.

The situation was ripe for change. In the 1970s a number of U.S. industries, such as those producing brand name luxury goods, agricultural chemicals and pharmaceuticals, began lobbying hard for stronger IPR, both at home and abroad, and gained an important voice in setting the U.S. legislative agenda. For instance, in the context of the fear about the loss of competitiveness, the 1979 amendments to Section 301 of the 1974 Trade Act allowed private parties to participate in the enforcement of existing trade agreements, and a key feature of those amendments was to require the federal government and the U.S. Trade Representative (USTR) to "take account of the view" and to "seek information and advice" from private sector representatives. As Sell (2003, 78) remarks: "the 1979 amendments significantly enlarged the scope of private sector participation in trade policy". While the voice for greater IPR was now being heard in trade policy, the same voice also gained authority on domestic issues in favor of extending and intensifying IPR. The IPR regime was about to transform.

In 1980, the U.S. Supreme Court, influenced by the increasing mood swing of U.S. authorities in favor of IPR, signaled a new attitude towards patents with two rulings. First, in the case of *Diamond v. Chakrabarty*, the U.S. Supreme Court allowed the patenting of a life form, which was crucial for the development of R&D in biotechnology (see Loeppky 2005, 75; Dutfield 2003, 154-6). Second, in the patent infringement suit of *Dawson Chem. Co. v. Rohm & Haas Co.*, the Court stated that "the policy of free competition runs deep in our law [...] but the policy of stimulating invention that underlies the entire patent system runs no less deep" (quoted in Sell 2003, 67). With this ruling, the Supreme Court ended the era of antitrust sentiment towards patents in the judiciary and placed the public policy of supporting patent rights on an equal footing with the public policy of supporting free competition (May

and Sell 2006, 141). The trend thickened in 1982, when the case *General Motors v. Devex* brought another landmark decision by the Supreme Court. The patent owner, who prevailed in the decision, received compensation for damages back to the date of infringement, as opposed to the date of judgment as in previous cases (Sell 2003, 70). This decision largely increased the expected compensation for patent owners wishing to enforce their rights.

The main judicial transformation in favor of IPR was the creation in 1982 of the Court of Appeals for the Federal Circuit (CAFC), sometimes called the "Patent Court". There are eleven circuit courts in the U.S., and to reverse a court decision related to a patent case in the appellate system, one previously had to choose among the eleven circuits. The problem was that there was no uniformity in the way each court of appeal enforced patent law. For example, between 1945 and 1957, patent rights were four times more likely to be enforced in the Seventh Circuit than in the Second Circuit (Sell 2003, 68). This situation occasioned both infringers and patent holders to "shop around" for a court conducive to their interests. The creation of the CAFC centralized the domestic judicial process for patent law and managed to put in place a decisive pro-patent orientation in the enforcement of the law. Some authors consider that this trend was due to the regulatory capture of judicial courts by corporate interests. For example, Drahos and Braithwaite (2002, 162) suggest that the idea of CAFC was pushed by a small group of firms and lobby groups in telecommunications, computers and pharmaceuticals interested in a different version of patent justice. Dreyfuss (1989, 28) argues that "the CAFC's leanings towards patentees may not be so much evidence of capture as recognition of national priorities", whereby stronger IPR would lead to greater national competitiveness. Whatever the explanation, the CAFC had a decisive impact on the enforcement of patents in the United States. For example, in patent infringement suits

between 1940 and 1949, circuit courts of appeal held patents to be invalid about 80% of the time. By contrast, after 1982, a patent infringer had only a 7% chance of reversing the decision in the newly established CAFC (Drahos and Braithwaite 2002, 162). CAFC invigorated the presumption of validity of patent rights. It shifted the burden to those wishing to infringe on patents to show that the patent was invalid, as opposed to patent holders having to prove their validity. The CAFC also raised the costs of infringement, and, it is worth noting, any reference to patents in terms of "monopolies" completely disappeared under the CAFC (Sell 2003, 70), which weakened antitrust arguments in court cases over patent infringement.

The new legal environment was a cause for celebration for patent lawyers, since the CAFC created almost from the ground up a multibillion-dollar patent litigation market. Drahos and Braithwaite remind us that patenting is a rich company's game, since few companies can afford the litigation costs related to patent disputes. Dominant companies know how much power a vast web of patents can thus bring in order to develop their earning-capacity by restraining competition (Drahos and Braithwaite 2002, 162):

> The kind of odds the CAFC hands out to alleged patent infringers increases the bargaining power of owners of large patent portfolios. It is a private bargaining power, used behind the curtain of commercial-in-confidence, making its effects hard to measure. Bargaining can easily stray into bullying when one side has so many intellectual property levers at its disposal.

According to Figure 6.1, those legal changes in the beginning of the 1980s correspond to the years during which we observe a significant increase in differential ROR for pharmaceuticals as compared to other manufacturing sectors. The surge of partnerships with

public institutions and the strengthened enforcement of patent rights allowed this sector to transform in such a way that dominant firms could substantially increase their goodwill, in the Veblenian sense.

These regulatory transformations continued the extension of patent rights in the 1980s, for example, by the continuing commodification of academic research, and the intensification of enforcement in courts. The Stevensen-Wydler Act was reinforced in 1986 with the Federal Technology Transfer Act and the Presidential Executive Order 12591 in 1987, which both encouraged and increased technology transfer from public institutions to private firms. The Bayh-Dole Act was also reinforced in 1983 after President Reagan's memo on patent policy, which extended benefits to dominant firms. The cooperation between universities and industry was enhanced by the 1984 National Cooperative Research Act, which afforded a special antitrust status to R&D joint-ventures by legalizing joint R&D efforts by firms in the same industry. Previously, such joint R&D efforts were judged inappropriate and universities could not collaborate simultaneously with different firms on the same project. By allowing joint-ventures between firms in their collaboration with universities, the 1984 Act enabled broad government-industry-university collaboration and funding over R&D projects (Slaughter and Rhoades 1996, 320). This legislation was central to the development of the web of cooperation agreements that emerged in pharmaceuticals in the 1980s. The weakening of antitrust laws continued with the 1993 National Cooperative Research and Production Act and the 2004 Standards Development Organization Advancement Act. Tax incentives for R&D were offered with the 1981 Economic Recovery Act, and pharmaceutical firms benefited further from the 1983 Orphan Drug Act, which provided tax credits and greater monopolies for innovations concerning rare diseases.

In the case of pharmaceuticals, the intense lobbying by the industry and its success in obtaining favorable legislation led generic manufacturers to develop their own capacity to confront growing rights of patent holders. The main legislative success for generics manufacturers, represented by the Generic Pharmaceutical Industrial Association (GPIA), was a piece of legislation that also managed to serve the interests of brand name pharmaceutical firms: the 1984 Drug Price Competition and Patent Term Restoration Act, also referred to as the Waxman-Hatch Act. The Act came as a congressionally supervised compromise between the GPIA and the Pharmaceutical Manufacturers Association (PMA, later PhRMA). Generics firms obtained the ability to obtain from the FDA faster and cheaper approval for their generic versions of existing drugs, while brand name manufacturers obtained an extension of their patent protection for up to five years (for a maximum of fourteen years) to compensate for the delays necessary to obtain FDA's marketing approval (Dutfield 2003, 120-1). The result was an effective extension of patent protection in pharmaceuticals. Table 6.4 sums up the main domestic legislation increasing differential ROR one way or the other for dominant pharmaceutical firms since 1980.

Table 6.4: Selected Legislation Enabling a Competitive Research and Development Policy for U.S. Big Pharma in the 1980s

Year	Legislation	Effect
1980	Stevenson-Wydler Act	Increases technology transfer from public organizations to private firms
1980	Bayh-Dole Act	Increases patenting of public research to accelerate technology transfer to private firms
1981	Economic Recovery Tax Act	Extends tax credits to companies for their R&D efforts
1982	Court of Appeals for the Federal Circuit	Increases the enforcement of patent rights and raises costs of infringement
1983	Orphan Drug Act	Provides tax credits and greater monopolies for innovations concerning rare diseases
1983	Memo on Government Patent Policy	Generalizes the advantages of the Bayh-Dole Act to all firms
1984	National Cooperative Research Act	Affords a special antitrust status to R&D joint-ventures among companies
1984	Waxman-Hatch Act	Extends up to five years patent protection for delays necessary for FDA approval
1986	Federal Technology Transfer Act	Increases technology transfer from public organizations to private firms
1987	Presidential Executive Order 12591	Increases technology transfer from public organizations to private firms

Source: Adapted from Coriat and Orsi (2002) and Slaughter and Rhoades (1996)

The main purpose of this series of legislation was three-fold: to encourage the commodification and the privatization of knowledge produced from public funding so it could increase high-technology firms' competitiveness; to provide tax incentives for greater

R&D; and to transform and reinterpret patent laws in a way that better serves the interests of patent holders in order to encourage R&D. The result was that, between 1983 and 1989, the acquisition of pharmaceutical patents by American firms increased by 125% according to the USPTO. The main consequence of this series of legislative acts was, however, to weaken antitrust laws considerably by providing huge monopolistic power to dominant corporate interests. Patent laws now supported almost any corporate strategy creating value based on the appropriation of knowledge, and turned a blind eye to monopolistic practices, pseudo-cartels and oligopolistic cooperation. Under the Reagan Administration, from 1980 to 1988, IPR became the 'magic trump card' that could allow previously suspect arrangements to proceed without being challenged by antitrust authorities. The 1980s has thus been referred to as the "anything goes era" for IP licensing arrangements (Sell 2003, 74).

The new IP regime in the United States was the symptom of a major shift in ideology towards corporate monopoly power. While the latter had been understood as an obstacle to social well-being and tight policies had been erected to limit such power since the 1940s, it was now considered to be a basic feature of a competitive economy. In 2000, Larry Summers, U.S. Treasure Secretary, synthesized the new ideology towards high-technology industries: "The only incentive to produce anything is the temporary possession of temporary monopoly power... without that power, the price will be bid down to marginal cost and high fixed costs cannot be recouped. So the constant pursuit of that monopoly power becomes the central driving thrust of the new economy" (quoted in *The Economist* 2000, 33). Monopoly was not an obstacle to the free-market anymore; it was now the "driving thrust" for the competitiveness of the U.S. economy. And while the regulatory regime was transforming, in

order to increase monopolistic capacities, differential ROR continued to escalate for pharmaceutical firms.

6.4 The Global Hegemony of IPR

While pro-IPR regulations came to transform the U.S. institutional structure, another problem was to implement global pro-IPR regulations, in order to defend U.S. market shares in the global economy. Japan was already dominating the global consumer electronics market, important market share was being lost in pharmaceuticals (see Chapter 4), and both politicians and academics were predicting imminent U.S. deindustrialization. For example, Sol Chaikin (1982, 848), from the International Ladies' Garment Workers' Union, wrote in *Foreign Affairs*:

> Because there are relatively few well-paying jobs in the services sector, an economy devoid of manufacturing would also necessarily experience a general decline of living standards [...] Unrestricted trade and the investment practices of the multinationals [...] can only lead to an America ultimately devoid of manufacturing.

In the same way, during the 1984 Presidential election campaign, the Democratic candidate Walter Mondale invoked images of Americans reduced to flipping burgers at McDonald's while the Japanese took over the country's industries (Bhagwati 1989, 445). National restructuring to increase economic competitiveness was not enough, the U.S. had to discipline other countries. And the chosen way to do so was to implement an international pro-IPR agenda.

For the most developed countries, it was not difficult to convince them of the benefits of such an agenda. In fact, the success of the new IP regime in the U.S., with increasing profits and capital accumulation for knowledge-based firms, was perceived across developed countries as a new route for greater competitiveness. Silicon Valley became the *nec plus ultra* of the emerging knowledge economy. Economic literature about new growth theories (Romer 1986; Lucas 1988) helped spread the idea that knowledge and technology were now the main sources of wealth. The new U.S. IP regime quickly became the "American model", which the rest of the world had to replicate to maintain its competitiveness. Encouraged by the OECD (Mörth 1998), the model of the knowledge-based economy became the new recipe for success in the era of global competitiveness (Cerny 1995). Most developed countries quickly picked up the same strategies and began providing tax incentives for R&D, increasing technology transfer from public research to private companies, and extending their IP protection standards. Manuel Castells (2000, 69) stresses that it was the state, with its development of large markets and macro-research programs, that "both in America and throughout the world, was the initiator of the information technology revolution".

Nevertheless, as long as the IP regime was confined to the domestic arena, its capacity to increase national competitiveness in pharmaceuticals remained limited, since patent infringement could happen abroad. Specifically, if developed countries might have had a profit incentive to implement strong IP policies, developing countries did not have any incentive to more aggressively protect the inventions that were mostly held in foreign countries. Furthermore, the existing global IP agreements were managed by the World Intellectual Property Organization (WIPO), a specialized U.N. agency in which each nation has one vote. Since developing countries formed the majority of nations, WIPO was not a

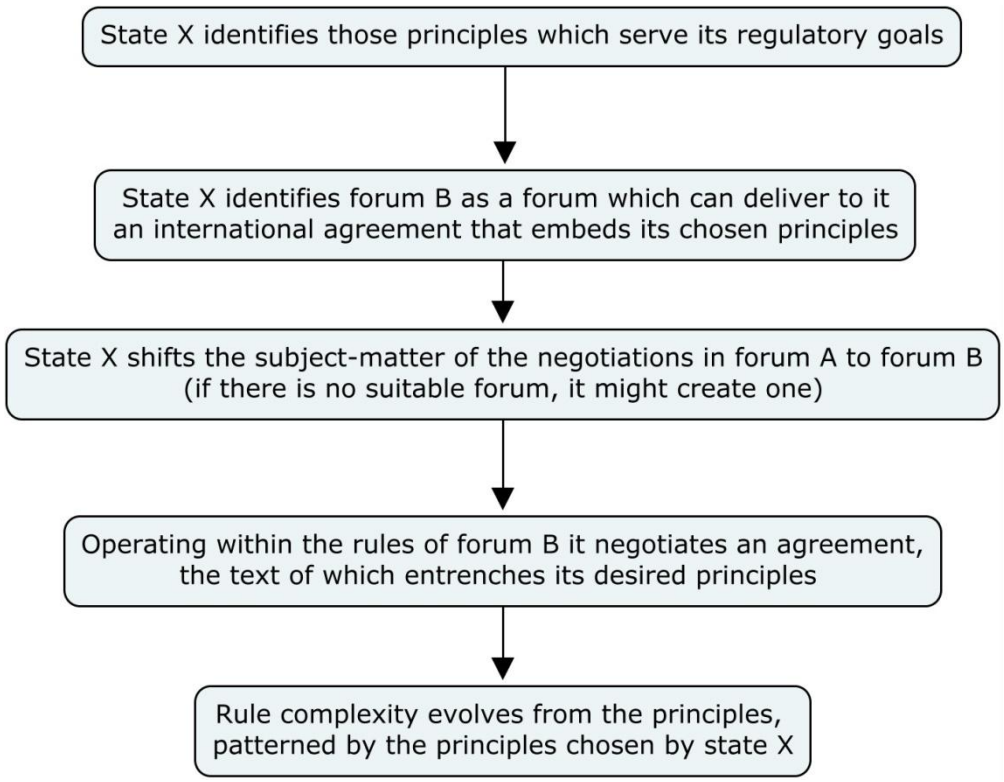
proper forum to develop further global IPR, and the organization was more disposed to encouraging technology transfers to developing countries than increasing the royalties of patent holders. In this sense, it was a 'tour de force' on the part of the U.S. pharmaceutical business when it effected the implementation of new global IP standards within the Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreement, which was ratified in 1994 at the end of GATT's Uruguay Round. A large literature exists on the process that brought about the ratification of TRIPs, which cannot be wholly summarized (for example Santoro 1992; Correa 1996; May 2000; Braithwaite and Drahos 2000; Sell 2003). However, it is necessary to recall the main aspects of this process, since U.S. pharmaceutical firms played a hegemonic role in the establishment of global IP standards. The primary role of Big Pharma in the implementation of TRIPs should not be surprising, since the protection of patents is essential for this industry. Bessen and Meurer (2008, 109) found out that more than one-half of the value of worldwide patents accrues to a small number of dominant pharmaceutical firms. The implementation of global IPR is thus directly linked to the evolution of differential ROR in pharmaceuticals.

Hegemony, Lobbying and Forum-Shifting

The concept of hegemony, defined as the capacity of a dominant group to rule with some degree of consent from the subordinate, has been discussed at length in the field of international political economy (for example Keohane 1984; Cox 1987; Gill and Law 1989). Most authors, however, have focused on the actors and the content of hegemony, and little has been written about how hegemonic actors succeeded in entrenching their own interests into hegemonic global norms. Braithwaite and Drahos (2000) studied at length empirical

cases of the negotiation process that led to the creation of global norms. This process is a prime example of how hegemonic actors can shape global norms. According to their findings, the global hegemony of the United States results mostly from its strategic capacity to go forward with its agenda by exploiting the disparities and divides within different global fora. Drawing on Michel Foucault and Bruno Latour, they reject the standard definitions of realist power and suggest that when the time comes to produce global norms and regulation, power is exercised by enrolling the capacities of others to its purposes; power is diffused by the actions of chains of agents, each of whom 'translates' it into his/her own uses, which can even mean that power can escape the complete control of the powerful (Braithwaite and Drahos 2000, 482). This complexity in the diffusion of power, or of rules, makes the powerful only able to influence action, not to impose their sovereign will. In fact, according to Braithwaite and Drahos' empirical findings, power seems to them the ability to "grab hold of", to "bundle" circulating resources much more than the capacity to coerce and impose. For instance, their findings consider *forum-shifting*, the ability to set negotiations in forums that best serve your interests, to be the prime strategic vehicle for the powerful to produce global norms according to their interests. Figure 6.4 illustrates a sequence of forum-shifting.

Figure 6.4: A Sequence of Forum-Shifting



Source: Braithwaite and Drahos (2000, 570).

Of interest in Braithwaite and Drahos' findings is that in rejecting the realist concepts of power, they also have to reject the concept of states as unitary actors (like billiard balls pushing each other around). Following Giddens (1984), they suggest that state power is best viewed not as statically structural but as emerging from a process of structuring (Braithwaite and Drahos 2000, 479). The state itself is made up of a multitude of controlling networks and divides, in which regulatory power constantly evolves and transforms among chains of actors. In a nutshell, not only do states use the forum-shifting strategy, but private actors 'under' the state attempt to capture domestic regulatory authority and direct its international

influence. In this way, state power is not exercised by a sovereign will, but, instead, by the most influential actors capable of capturing and orienting power in the desired direction through lobbying efforts.

Big Pharma is considered Washington's largest lobby (Public Citizen 2001b). According to the Center for Public Integrity (CPI), the pharmaceutical lobby spent $168 million in lobbying efforts in 2007, of which 125 million was spent by the firms of Big Pharma (Ismail 2008), and more than $1 billion in the previous decade. According to lobbying disclosure reports filed with Congress, drug firms lobbied on an array of issues, from the deregulation of advertising to the extension of Medicare coverage, but the three main issues on their lobby agenda have been 1) blocking the importation of inexpensive drugs from other countries; 2) extending pharmaceutical patents in the U.S. and abroad; and 3) influencing the content of free-trade agreements (quoted in Ismail 2008).

Because of the primacy of businessman in the social order of the Twentieth Century, Veblen (1923, 37) concluded that the state was nothing less than an instrument in the hands of dominant corporations: "So the constituted authorities of the [U.S.] democratic commonwealth come, in effect, to constitute a Soviet of Business Men's Delegates, whose dutiful privilege it is to safeguard and enlarge the special advantages of the country's absentee owners." The case of TRIPs is a landmark example of how private actors, mainly pharmaceutical firms like Pfizer, managed through political lobbying to grab hold of state mechanisms and use the international influence of the U.S. to pressure for new global regulations that served their own interests. In this way, strategic lobbying and forum-shifting became the ways and means of an emerging global hegemony of IPR.

Private Power and Public Law; How Pfizer Establishes Global Rules

Pfizer began lobbying for higher global IPR standards in the 1970s. With manufacturing facilities in many developing countries, such as Argentina, Mexico, Korea, Brazil, Indonesia, Taiwan, Thailand and India, Pfizer got seriously involved in political lobbying when Edmund Pratt became CEO in 1972. Patent enforcement was too weak in most developing countries, and Pfizer determined that it was losing too much market share to developing countries' generics manufacturers. As such, developing countries had to be disciplined. At first, Pfizer operated through persuasion, and went into every forum to press its position (Santoro 1992, 461). WIPO, in which developing countries formed the majority, was the main global forum for discussing global IP principles. Pfizer's efforts at WIPO in the beginning of the 1980s were totally fruitless, according to Pfizer's general counsel Lou Clemente (quoted in Santoro 1992, 462): "Our approach to WIPO was a disaster. As a UN organization, WIPO works by majority, and, simply put, there were more of them than us. Our experience with WIPO was the last straw in our attempt to operate by persuasion". Under the leadership of Edmund Pratt, Pfizer sought new avenues through which to implement new IP standards. After the failure at WIPO, Barry MacTaggart (1982), Chairman and CEO of Pfizer International, published an aggressive op-ed piece in the New York Times against the organization and its lax patent protection, titled "Stealing from the Mind". Pfizer invited its managers in developing countries with low patent protection to get involved with local business, professional, academic and government groups to build a consensus in favor of stronger IPR.

Pfizer executives also played key roles in business organizations in developed countries (Santoro 1992, 463): Pratt was appointed to President Carter's Advisory Committee on Trade

and Policy Negotiations (ACPTN) in 1979, and became the organization's Chairman in 1981; he also headed the Business Roundtable of 200 CEOs. Gerald Laubach, then President of Pfizer, sat on the board of the PMA (now PhRMA), as well as on President Reagan's Council on Competitiveness. Lou Clemente, Pfizer's General Counsel, was head of the Intellectual Property Committee of the U.S. Council for International Business, while Pfizer's Vice-President for Public Affairs headed the Council's Committee for Europe. President of Pfizer International's, Barry MacTaggart, was involved with the U.S.-India Business Council, while his successor, Bob Neimeth, became Chair of the Trade Committee for the Business and Industry Advisory Committee. Some of Pfizer's executives were also involved in the National Foreign Trade Council and the U.S. Chamber of Commerce. With so many agents in most U.S. business forums, building a consensus in favor of a stronger IP regime was relatively easy within the U.S. business community. Developing countries that were operating under existing international IP standards now became "pirate states" in the U.S. business community's vocabulary.

After the WIPO failure, Pfizer strategists looked to shift the IP issue to a new and more business-friendly forum. Their idea was to link IP with investment, in order to implement an IP clause within an investment agreement. Here, they pushed for a global Multilateral Agreement on Investment (Drahos and Braithwaite 2002, 62), but this was soon estimated to be politically out of reach. Pfizer then developed a second and more radical idea: linking investment to trade (Drahos and Braithwaite 2002, 68). This new approach suggested that an effective trade regime had to liberalize the opportunities for global investors, which implied that global IP standards were necessary to protect such investments. This paradigm shift permitted the link between the extension of monopolistic capacities with negotiations aimed

at trade liberalization; two elements that, by definition, do not match. It also allowed taking global IP negotiations out of WIPO, in order to embed it in the GATT trade negotiation forum.

On the national scene, Pfizer's influence in policy-making circles grew enormously. In 1984, the Assistant Secretary of Commerce and Commissioner of Patents and Trademarks, Gerald J. Mossinghoff, on behalf of the Reagan Administration, delivered a major speech outlining the importance of linking patents and international trade: "There is widespread bipartisan agreement that the protection of intellectual property worldwide is a critically important factor in expanding trade in high technology products. This Administration is committed to strengthening that protection as an integral component of our service to US trade and industry" (quoted in Sell 2003, 83). One year later, Mossinghoff became President of PMA (later PhRMA). In his February 1986 message to Congress entitled "America's Agenda for the Future", President Reagan proposed that a key item for U.S. competitiveness was the protection of U.S. IPR abroad (Drahos and Braithwaite 2002, 116).

The main problem, however, was that other developed countries, while implementing pro-IPR agenda in their national economy, were simply not interested in increasing global IP standards. One month after the speech, the Reagan Administration created the Intellectual Property Committee (IPC), a group of 13 CEOs from IP-related sectors, headed by Edmund Pratt of Pfizer and John Opel of IBM, and including the CEOs of Bristol-Myers, DuPont, J&J, Merck and Monsanto. The IPC's role was to provide private sector input to the U.S. Trade Representative (USTR) and to monitor trade negotiations (Santoro 1992, 465). The IPC also played a very important strategic role in gaining the support of the other Quad countries (Europe, Japan and Canada), by forging alliances with their respective business

communities. With the support of those foreign business communities, the IPC managed to organize the Tripartite Coalition, a global pro-IP business lobby formed by the IPC, the Union of Industrial Employers' Confederation of Europe (UNICE) and Keidanren, a private federation of economic organizations in Japan. All groups succeeded in convincing their respective governments to include IP protection in the agenda for the GATT negotiations.

In September 1986, the Punta del Este GATT's ministerial conference launched a new round of negotiation for trade liberalization: the Uruguay Round. Pfizer's CEO, Edmund Pratt, attended the meeting as Chairman of ACTPN, and headed a group of private sector advisers in the U.S. delegation. Pratt, with the IPC and Tripartite Coalition, pushed hard on developed countries and succeeded in including in the Uruguay Round agenda negotiations on the Trade-Related Aspects of Intellectual Property (TRIPs) (Santoro 1992, 468). In November 1986, the members of the Tripartite Coalition met in order to develop the framework of a multilateral agreement that would propose "minimal" global IP standards and that could be used as a guide in the negotiations. In June 1988, the Tripartite Coalition arrived at a consensus on global IP rules and published what it called the "Basic Framework", which Edmund Pratt considered a "multilateral blueprint" for trade negotiators (Drahos and Braithwaite 2002, 123). The CEOs of the IPC described the document as the result of actions within the "international business community". John A. Young, CEO of Hewlett-Packard, explains: "The 'Basic Framework' [was] unprecedented. [It was] the first time that the international business community has jointly developed a document of this magnitude and such substantive detail for presentation to our government negotiators" (quoted in Santoro 1992, 467).

Special 301: How the U.S. Served the "International Business Community"

Drahos and Braithwaite (2002, 125) suggest that the "Basic Framework" was in many ways the seminal document of the TRIPs negotiations: "It was a declaration of principles of property wanted by big business for the coming global information economy. A member of the IPC claimed that it established the US negotiating position. There is little exaggeration in this claim." The IPC thus managed to create a consensus in the "international business community" about a pro-IP agenda in trade negotiations, got developed countries' administrations to defend that agenda, and oriented the content of the principles to be defended. The main problem remained that multilateral trade negotiations included many developing countries that had no interest in increasing global IP standards. Developed countries could propose trade leverage, for example, by promising reductions in farm subsidies in exchange for the ratification of TRIPs. Such carrots, however, were far from enough, and a huge stick was necessary to discipline developing countries. In order to render such a stick, the U.S. passed the 1988 Omnibus Trade and Competitiveness Act, giving greater unilateral authority to the USTR to retaliate against foreign practices that were judged harmful to U.S. trade. The Act included the "Special 301" clause, requiring the USTR to publicly identify foreign states that denied IP protection to U.S. firms and to list the most important infringing countries as "Priority Foreign Countries", which would then be investigated in order to determine if unilateral U.S. trade sanctions should be applied. Under the Act, sanctions would be justified not only with infringement of existing trade or IP agreements in a manner detrimental to U.S. corporate interests, but also when a country merely acted in compliance with existing international trade law. The implementation of the Special 301 clause was a forceful signal for the rest of the world to match U.S. domestic IP

standards. Since the USTR needs to rely on inputs from the business community (the IPC) to list "rogue" IP countries, the Special 301 allows U.S. corporate interests to capture U.S. state power, by sanctioning disagreeable foreign practices. As one lawyer from a multinational explained to Braithwaite and Drahos (2000, 79):

> The 301 process was highly effective because once tariffs were imposed on a developing country's imports into the US those tariffs 'killed their markets' and in many cases the developing country would never recover its previous market share. In the face of such coercion, the value of non-compliance with US demands on intellectual property by developing countries plummeted dramatically.

Another dimension of the Special 301 merits note. The publicization of the "Priority Watchlist" is nothing less than a public threat to retaliate against a country. Since most countries on the planet have an important trade surplus with the U.S., the possibility of losing that market can make local investors extremely nervous, and even the small probability of U.S. sanctions can reduce investments and create economic instability in the national economy. The threat of sanctions can thus be as efficient as the sanctions themselves.

The case of Thailand can help us better understand this disciplinary power of U.S. corporate interests against 'contravening' countries. In April 1991, the USTR named for the first time three nations –India, China and Thailand– as "Priority Foreign Countries" under Special 301 because of inadequate protection of pharmaceutical patents. Thailand had a surplus of $2.7 billion with the U.S., which was the destination of 25% of Thai exports. Thai authorities thus took such threats very seriously. In 1992, after the required investigation, the U.S. explicitly threatened with limiting textile imports from Thailand. Thai authorities proposed implementation of a new Patent Act, in order to strengthen IPR in the country and

lift the threat of unilateral trade sanctions by the United States. In September 1992, however, the Thai Supreme Court issued a report entitled "National Experience on Judiciary and Intellectual Property System" that harshly criticized the new Patent Act. It stated, "Thailand is not ready to change and improve the level of (pharmaceutical) patent protection," moving from its 1979 Act which "intends to protect the public" to the new Act of 1992 which "aims to protect the inventors." The report claimed that Thailand was being forced by "countries that own technologies of producing pharmaceutical products to improve patent law for the exchange of trade benefits" (quoted in Markandya 2001). Nonetheless, two weeks later, the new Patent Act was implemented.

Drahos and Braithwaite (2002, 61-149) explain at length how the forum-shifting process successfully continued for the "international business community". Forum-shifting was not only the shift of the IP issue from WIPO to GATT, it was a continual process of negotiation and consolidation of the IP global agenda through the shifting from business forums, such as the ACTN and IPC, to international forums such as the Quad, G-7, GATT and the negotiations of bilateral agreements. TRIPs was finally ratified in 1994, encompassing most of the 'Basic Framework' provided by the "international business community" of the Tripartite coalition. Three main elements brought about the ratification of TRIPs in 1994: 1) the strong lobbying of the U.S. pro-IP business community that captured part of the agenda of the USTR, using state power and hegemonic influence to establish higher international IP standards; 2) the capacity of the American business community to influence other business communities in developed countries (mainly through the IPC); and 3) the Special 301 that allowed unilateral sanctions on those countries not acting in a manner conducive to U.S.

corporate interests. Building on the concepts of *imperium* and *dominium* put forth by Cohen (1927), Braithwaite and Drahos (2000, 84-85) conclude:

> Actors within the US form an alliance to achieve a new global dominium over abstract objects, a dominium, that has important implications for the US imperium. (...) TRIPs, one might say, helps to institutionalize proprietorial powers over the kinds of abstract objects in which the US has a human capital advantage. (...) US intellectual property exporting firms called on the coercive power of the US state to play for and win an expanded frontier in the property of knowledge in 1994.

The capture of state capacity, in order to enforce greater monopolistic capacities for innovative sectors has been central in implementing and enforcing global IP-regime standards serving the vested interests of Big Pharma. Note that TRIPs did not directly provide much greater markups for Big Pharma, it served mostly to discipline developing countries, by forcing them to implement minimum standards in pharmaceutical patent protection, even though such standards did not have to be implemented before 2005 for most developing and emerging countries[70]. TRIPs thus had little direct impact on Big Pharma's earning-capacity and differential ROR before 2005. However, the ideological dimension of TRIPs was very important for Big Pharma's interests, since it allowed a global dissemination of the "imperatives" of enhanced IP protection, making resistance or alternative points of view more difficult to defend or express. TRIPs transformed the institutional setting of debates and struggles around the IP issue. The ideological impact is enormous − if all countries acknowledge the necessity of greater IP protection, then anti-IP movements and free culture advocates can only be seen as radicals, or, as Microsoft's CEO Bill Gates likes to call them, "modern-day sort of communists" (quoted in Andrews 2005).

[70] TRIPs standards for pharmaceutical patents had to be implemented by 2005 in developing countries and by 2016 in least developed countries.

The story of TRIPs clearly shows an example of how private actors managed to transform their "needs" into a set of global standards imposed on reluctant actors. It shows how a specific discourse, serving specific vested interests, can become a hegemonic global norm, an institutional constraint or, as Veblen would put it, a shared habit of thought. It also shows how private actors compete not necessarily to develop processes of production that are less costly, but rather to transform power structures to their advantage. The success of TRIPs for Big Pharma has been two-fold: 1) by implementing patent protection in most developing countries, it has increased the differential markups for medications since that year; and 2) it established a new global norm based on the necessity of increased IP protection, which allows Big Pharma to advance its interests within each member states and in future agreements. TRIPs increased not only Big Pharma's monopolistic capacities and differential ROR, but also its ideological influence over the whole power structure. It entrenched, or institutionalized, the idea of a global "information age", and that the rules of free trade had to change accordingly. It promoted the idea that production was now based on intangible assets producing immaterial goods and that measures had to be taken worldwide to assure that greater investments in innovation would be followed by greater profits.

6.5 More Patents, More Profits, Less Innovation

> « The Public will learn that patents are artificial stimuli to improvident exertions; that they cheat people by promising what they cannot perform; that they rarely give security to really good inventions, and elevate into importance a number of trifles […], no possible good can ever come of a Patent Law, however admirably it may be framed. »
>
> -*The Economist*, 1851

Increasing IP standards, both nationally and globally, created new rent-seeking capacities and monopolistic power for dominant firms. They transformed the favored paths to differential accumulation by proposing new ways to enhance differential depth. In the *Economic Report of the President 2006* (219), it is asserted that, in the U.S., the intellectual property industries represented 17.3% of total value added. Furthermore, intellectual property assets represented a third of the combined market value of American corporations (220), other intangible assets (or knowledge capital) represented 38% while tangible assets represented only 30% of that market value. According to the think tank *USA for Innovation*, IPR are worth about 24% of the value of the U.S. economy (Shapiro and Hassett 2005, 18): "Assuming that the stock of U.S. intangible business assets already approximates the stock of tangible business assets, then business knowledge capital is worth $11.7 trillion, and intellectual property would comprise 47 percent of that total or $5.5 trillion." Moreover, *USA for innovation* considers that, in general, all companies' profitability depends increasingly "on the depth and quality of its intellectual property", linking the firms' ability to succeed in a highly competitive global environment with the strategic value of their IPR portfolio (Shapiro and Hassett 2005, 19). Patents have thus become the new gold rush (Economist 2000), and they have transformed the knowledge structure and business practice upon which the pharmaceutical industry proceeds.

Rushing for Patents, Any Patent

According to the USPTO, between 1979 and 2006 the annual number of patents issued in the U.S. grew by 256%. According to WIPO, the number of global patents issued under the Patent Cooperation Treaty grew by 6020% between 1980 and 2007, a yearly growth of

16%. According to the OECD, the ratio between the number of patents issued by the European Patent Office and European R&D spending grew by 50% between 1982 and 2000 (Kahn 2008), showing that firms obtain more patents per dollar spent in R&D. In the case of pharmaceutical patents, the trend was particularly striking. In the U.S., yearly issued patents on drugs went from 754 in 1979 to 3262 in 2006, an increase of 333%. According to WIPO, the trend continues as strong as ever: global patents on pharmaceuticals, cosmetics and biotechnology, which represent 9% of all patents issued, went from 14 259 in 2000 to 21 560 in 2007, an increase of 51%.

However, while this gold rush continues, a growing academic literature complains that patents issued are often of poor quality: patents are often too broad in the scope of what they are protecting or simply should not have been issued, since the innovation is often worthless. While there is a formal process to examine patents, the surge in patent filing and the growing complexity of numerous claims of novelty made by patentees has deteriorated the quality of examination each filing. Examining how the U.S. patent system is now stifling innovation, Jaffe and Lerner (2004, 142) explain:

> [In] practice the system seems more akin to a registration system: in many cases it appears that a determined patentee can get almost any award he seeks. [...] This is the predictable result when underpaid, inexperienced, and overworked examiners are pushed to resolve cases as quickly as possible, and are given flawed and obsolete tools for finding and searching the prior art.

In the case that a request for a patent is rejected, the applicant can re-submit his request. As many as 25% of ‘new’ applications are, in fact, resubmitted filings that have been previously rejected (Quillen and al. 2002). Furthermore, since 2008, a website has been put

up by private actors (www.usptoexaminers.com) to assess USPTO examiners, enabling them to "shop around" for an examiner more likely to approve their application.

Granting more patents of lower quality does not necessarily encourage innovation. On the contrary, when technologies are complex and the standards for issuing broad patents are low, a situation emerges in which a multitude of patents relate to every single new technology, forcing any innovator to share their benefits with a pool of patent holders and deterring incentives for innovation (Bessen 2003). In fact, the race for patents has become a race for strategic patenting, a strategy consisting of patenting as many elements as possible in their broadest scope, in order to provide patent holders greater potential rights over future innovations. Such patent portfolios allow the construction of "patent thickets", or "patent gridlocks" (Heller 2008a), which are barriers to entry based on the threat of patent litigations against any new competitors. As such, patents are used in business sectors less as an incentive to innovation than as a barrier to entry and restraint on competition.

Strategic patenting to obtain patent thickets made up of numerous low quality patents has brought about a "patent bubble" (Lallement 2007, 3) on both sides of the Atlantic, causing a decline in innovation. According to a German report by the Ministry of Economics and Technology concerning the relationship between patents and innovation (quoted in Lallement 2007, 4), actual trends in the multiplication of low quality patents cause serious harm to innovation. Instead of providing an incentive for innovation, the multiplication of patents has been such that potential innovators think twice before doing any research. For example, Peter Ringrose, former chief science officer at Bristol-Myers Squibb, claimed that his company would not investigate some 50 potential cancer-causing proteins, because patent holders would either decline to cooperate or demand large royalties (quoted in Heller 2008b).

Two Nobel laureates, Joseph Stiglitz and John Sulston,[71] have concluded that, because of the IPR regime, medical research is "hindered by out-of-date laws," and that obstructive patents on genes and medical techniques can in fact "impede innovation, lead to monopolization, and unduly restrict access to the benefits of knowledge" (quoted in Jenkins and Henderson 2008).

An important share of the cost of innovation now involves the assembly of dispersed bits of intellectual property and the acquisition of necessary licenses. For example, Nicholas Naclerio, former head of the BioChip Division at Motorola, has suggested that the surge in biotech patenting did not bring about therapeutic innovation but "a bewildering web of lawsuits – and it may only get worse". He continues, "If we want to make a medical diagnostic with 40 genes on it, and 20 companies hold patents on those genes, we may have a big problem. It isn't at all clear how this is going to work out" (quoted in Gibbs 2001). Heller and Eisenberg (1998, 698) define such underuse of a resource, when multiple owners each have a right to exclude others from that scarce resource, the "Tragedy of the Anticommons". For Heller (2008a), such examples show that if everyone invests in the litigation process, innovation is tossed aside, gridlock sets in, and many lose out, except dominant patent holders who are restraining innovation. Even gathering information about who owns relevant patents for a field of research can prove complex and expensive for small research labs. For example, it was reported that the University of Iowa had to contact 71 entities, because one of their small labs was working on a rare ocular disease (Heller 2008b).

[71] Joseph Stiglitz won the Nobel Prize in Economics in 2001 and John Sulston won the Nobel Prize for Medicine in 2002 for his work on genome sequencing. According to a press release by the University of Manchester (2008), they both participate in the University of Manchester's Institute for Science, Ethics and Innovation, where in July they launched a series of conferences about the ownership of science, with 40 leading scientists and ethicists from across Britain. The series of conferences should lead to the formulation of a 'Manchester Manifesto', which they hope will lay down a consensus on intellectual property in science. The Manchester Manifesto process was scheduled for completion in 2009.

The increasing number of patents also brings an increasing cost in patent litigation. According to André Choulika and David Sourdive, founders and directors of Cellectis, a French firm specialized in genomics, patent litigation is the sinews of war: "If we are not attacked, it is because we are not working on a good path" (quoted in Khan 2008, author's translation). In fact, researchers found out that patent litigation costs now outstrip profits coming directly from patents held by publicly traded United States companies (Bessen and Meurer 2007; 2008). Using calculations based on the behavior of patent owners and on the behavior of investors, Bessen and Meurer (2008, 95-146) managed to calculate the incremental market value of patents as compared to an economy where innovations are not patented. They show that the worldwide value of patents in 1999 was around $18 billion while the costs for patent litigation in the U.S. alone amounted to $16 billion. Legal procedures, however, are only the tip of the iceberg, since most litigation finds its solutions outside of courts in total secrecy (Kahn 2008).

Patent lawyers suggest the emergence of a "Patent Paradox" (Hall and Ziedonis 2001), pointing to an increasing patent intensity (number of patents per R&D dollars spent), coupled with the diminishing value of individual patents. The existing literature is often helpless to explain this situation. For example, Bessen and Meurer (2008, 104) argue that if innovators continue to patent their inventions, even when costs are outstripping benefits, it is because patentees are "irrational gamblers", willing to lose money on numerous patents for the chance to obtain a very lucrative one. Such insufficient explanations are based on standard economics, and the institutionalist approach offers a more relevant interpretation. The multiplication of patents should be more properly understood as part of a long-term accumulation regime. The "patent paradox" disappears if we consider that patents are mostly

used as strategic tokens of exchange between corporate entities, just as was the case in the 1930s (see Chapter 4). The true value of patents does not lie in their individual worth, but in their status as components of strategically developed portfolios (Parchomovsky and Wagner 2005, 51). Patent portfolios are thus managed as an important strategic asset in order to restrain competition or to negotiate with competitors for pseudo-cartel agreements through cross-licensing. For example, a patent portfolio can facilitate mergers and acquisitions by attracting external innovation and can prove useful to avoid patent litigation by creating the threat of "mutually-assured patent litigation". In turn, this can facilitate subsequent in-house innovation or force cross-licensing agreements (Parchomovsky and Wagner 2005, 33-8). *The Economist* (2000) underlines this point in an interview with Bob Bransom, a patent lawyer:

> "Everybody is infringing everybody's patents all the time," says Mr. Bransom. "So one guy puts a pile of papers five inches high on the table, and the other guys have a smaller pile." The defender then calls Mr. Bransom for help in buying some patents that the aggressor is infringing. The usual outcome is a cross-licensing agreement, with or without cash thrown in, depending on the relative size of the piles.

Patent pooling has thus made an aggressive comeback. Such pooling agreements through cross-licensing are generally mandatory for participants in recognized standard-setting organizations, such as computer technology or DVD technology (Boldrin and Levine 2008, 63), but they are also very common in the pharmaceutical business, as shown earlier by the large amount of cooperation agreements among Big Pharma. Boldrin and Levine (2008, 64) note that the widespread existence of patent pools in industries with a well-established set of mildly competing insiders is valuable evidence of two realities: "First, patents are inessential to compensating individual firms for the fixed cost of invention. Second, patents are a

powerful tool for establishing monopoly power and preventing entry by potential competitors".

Large firms thus have an incentive to patent more, even if the value of individual patents most of the time is less than their acquisition costs, since the marginal value of increasing the size and diversity of patent portfolio is much greater than the marginal value of the individual patent itself (Parchomovsky and Wagner 2005, 43). In fact, understanding patents through the lens of patent portfolios allows Parchomovsky and Wagner (2005, 60-66) to predict that trends in patenting will only intensify if nothing is done to modify existing business patterns. As such, the growing number of patent applications will continue to increase pressure on patent examiners, reducing the quality of individual patent examinations; patent thickets will continue to grow; patent litigation costs will continue to increase; cross-licensing arrangements will continue to proliferate; the patent system will increasingly favor dominant firms and the value of individual patents will become more obscure (and increasingly irrelevant). Those predictions have to do with all sectors but, considering that Bessen and Meurer (2008, 139) note that pharmaceuticals and chemicals are the main sectors enjoying considerable profits associated with worldwide patents, we must consider that those predictions apply especially well to those two sectors.

Under current business practice, patents are not considered incentives for innovation. Patents are amalgamated in bundles by corporate entities not only to appropriate and control existing knowledge, but also to deploy control over complete innovation paths, in a way that forces future innovators to pay them a share of the future profits. In this way, patents reduce the financial incentives for future innovation. With complex technologies, bundles of patents have become an important source of capitalist power for dominant firms and allow increasing

earning-capacities even when they are in fact slowing down innovation. The increasing control by private interests over the knowledge structure of pharmaceutical research through patent thickets must be considered central in the growing differential ROR for pharmaceutical firms since 1980.

The Me-too Business Model

The increasing quantity of patents and their decreasing quality also have other important impacts on the business model in which the pharmaceutical sector evolves. Specifically, the growing number of patents for lesser innovation allows drug companies to build-up an important portfolio of patents on trivial developments compared to existing products. As Carlos Correa (quoted in Dutfield 2003, 109) explains:

> Only a few (several dozen) 'new chemical entities [...] are developed and patented each year. Nonetheless, thousands of patents are granted annually in this sector. This paradox can be explained by the enormous capacity that the sector's major firms have built up not only for developing authentic inventions, but also for taking out patents on secondary, occasionally trivial developments, in order to extend their monopoly over a product or process, beyond that allowed by the original patent.

Since Big Pharma firms feed on "blockbusters", it should not be surprising that they try to stretch out their monopoly rights over their drugs as long as possible, especially since a small number of highly profitable products usually makes up the bulk of companies' revenues. A number of regulatory tricks exist to extend the validity of a patent in each country's patent system. For example, in the United States, the Waxman-Hatch Act increases up to five years patent protection to compensate for delay in the FDA approval process. Testing a drug for pediatric uses grants another 6 months extension to the validity of the

patent. Another way to prevent generic competition is to pay generic manufacturers in exchange for not marketing their products (Stolberg and Gerth 2000; Boast 2001; Dutfield 2003, 109-110; Carreyrou and al. 2006; Saul 2008). Collusive agreements between brand-name companies, or between a brand-name company and a generic manufacturer, are also on the rise to contain generic competiton by marketing "pseudo-generics", which are generic products that remain under the control of brand-name companies, in order to maintain their share of a market (Hollis 2003; Bloomberg 2005).

The main tactic, however, is to marginally improve "blockbusters", in order to obtain renewed patent protection over a slightly improved version of a compound. For example, a firm can obtain new patents by modifying delivery methods, reducing dosage regimens, developing new versions of the active compound with fewer side-effects, or combining two separate medications into a single dosage form. Such imitative products marginally improving existing drugs are referred to as "Me-too drugs" in the literature. As Merril Goozner (2004) has explained, for a growing number of critics, "me-too" drug development has come to dominate industry. While their incremental improvement or utility is usually very narrow, they can produce important commercial success. Many blockbusters, such as Zantac, Lipitor, Ritalin, Nexium, Paxil, Zoloft or Zocor, constitute little or no therapeutic advance on previous drugs. Ultimately, the commercial success of new drugs often does not depend on its medicinal novelty, and R&D is generally organized with an eye to commercial success, not therapeutic value.

For instance, when Prozac, a blockbuster manufactured by Eli Lilly, was about to lose its exclusivity in 2001, the company patented a new formulation, Weekly Prozac, which maintained exclusivity rights for Prozac until February 2004. Furthermore, because Prozac

was helpful in reducing symptoms of the premenstrual syndrome (PMS), Eli Lilly created a new drug, Sarafem, which was in fact the same drug as Prozac in an identical dose, but colored pink and lavender instead of green. Eli Lilly patented and advertised its "new" drug for a new condition: Premenstrual Dysphoric Disorder (PMDD). "Think it's PMS? It could be PMDD" says Eli Lilly's TV commercial in what is considered by many critics as a formidable example of disease mongering, a phenomenon in which drug companies promote new diseases for existing drugs, instead of new drugs for existing diseases (Moynihan and Cassels 2005, 99-118). Sarafem was priced higher than Prozac (same pill, same dosage, different color), and Eli Lilly thus managed to maintain a high price in a particular niche for its off-patent Prozac by persuading doctors to prescribe Sarafem for PMDD, instead of generic Prozac (Angell 2004, 189).

Pharmaceutical research is expensive and the creation from scratch of breakthrough products is a risky business. Indeed, the financial incentives for such R&D are, most of the time, simply not there, except maybe for chronic conditions, such as diabetes or obesity. The reasons for this lack of incentive lie primarily within the existing patent system: 1) the creation of patent thickets discourages truly innovative R&D, by raising the spectre of multiple lawsuits, especially in the case of biotechnologies; and 2) the permissive approval of patents makes "me-too" drugs as profitable as breakthrough products, even though they are less costly and less risky to develop.

Thus, the main business model adopted by pharmaceutical firms in terms of R&D and product development is to extend the longevity of patents on existing drugs by creating "me-too" drugs with low incremental therapeutic benefits. This is not to say that there was no breakthrough innovation in recent years, it is simply to make the point that the existing

model of innovation discourages it in favor of imitative drugs. Of all the new drugs approved by the FDA between 1989 and 2000, 77% were classified as offering little or no therapeutic gain (NIHCM 2002). The situation is identical in other countries: In Canada, according to PMPRB annual reports, only 5.9% of the 1147 new drugs approved between 1990 and 2003 were considered to be breakthrough products. In 2007, 141 new drugs entered the French market: 17 represented significant therapeutic progress, whereas 94 did not offer any therapeutic advantages compared to existing treatments, and 15 were labeled by the editors of an independent medical journal to be potential dangers to the public health (Prescrire 2008).

Pharmaceutical firms often assert that they do not have a choice in their research agenda, because the profits on me-too products are needed so that they can re-invest in breakthrough research. This assertion masks the fact that the ten most important pharmaceutical firms, from 1996 to 2005, had net returns on equity of 28%, with 77% of all net benefits being distributed to shareholders and another 16% of all net benefits being simply accumulated in the cash reserves of the firms (Lauzon and Hasbani 2006). This assertion is also contrary to economic theory since investment decisions concerning research must be based only on the expected returns of such investments, as compared to the expected returns from alternate use of the funds. Morgan et al. (2006, 23), analyzing the incentives for valuable innovation in pharmaceuticals conclude:

> The ability to earn monopoly profits from relatively low-risk and low-cost imitative research reduces the incentive for innovation because funding and scarce research inputs (expert personnel) are drawn away from potential riskier but more socially valuable research toward truly innovative drugs. [...] However *commercially* valuable imitative research may be, there is a *societal opportunity-cost* to research designed to invent around discoveries that have already been made. Scientists trying to discover a substitute invention for an existing product cannot simultaneously be working on other, truly innovative research efforts.

Interestingly, after publishing a small op-ed piece about the me-too business model in a biotechnology trade publication (Gagnon 2008b), this author received many e-mails from people in the industry, most of them primarily in agreement with the piece and telling their own story about innovation shortcomings in everyday practice. One message from a Senior Vice-President of a biotechnology firm was more critical since the person interpreted the piece as an accusation that firms' managers were making the wrong choices in terms of R&D decisions. His explanations were, in fact, confirming the argument that the knowledge structure of the industry is shaped by the financial incentives that discourage firms from pursuing truly innovative research:

> The money risks are so huge that everyone wants to wait for someone else to "de-risk" the project before putting serious resources behind it. This applies to start-ups, as well as internally inside of big pharma. [...] If I am a group leader inside of Merck/Astra-Zeneca/etc., my team might have ideas about an innovative approach to X, Y or Z. If we start from zero, we would probably need 2-3 PhD biologists and at least 6 medicinal chemists to make a dent in anything. We also need support from all kinds of other functions (analytical chemistry, x-ray crystallography, toxicology, metabolism, imaging, and animal models). We need a few million dollars per year for an unknown number of years. Maybe nothing will come of it. And, if nothing does, we are all likely to get laid off because our company (like all companies) is a results-oriented entity. Do I take my team out on that limb? Do I risk their futures and the financial security of their families – or do I elect to go after an improved proton pump inhibitor for gastroesophageal reflux disease? The likelihood of achieving that is immensely better than the likelihood of a breakthrough drug for Alzheimer's disease. If you had two young children – what would you do?

I replied to him that I had one young child and I would do exactly the same as him. Once again, it is not a question of leveling blame; it is a question of understanding the structural and regulatory environment, the power structures at play in the organization of production and the financial incentives they provide. Ultimately, the resulting knowledge structure in pharmaceuticals provides little incentives for greater innovation. The business model based

on me-too drug development must also be properly understood as very profitable. It maintains high levels of profit while reducing the cost of bringing new products on the market. Because of this business model, differential ROR can increase, not in spite of the decline in innovation, but because of it.

The analysis of differential depth showed how the surge in differential ROR that began in the 1980s was caused first and foremost by the national strategy to transform regulatory structures in order for the United States to regain its lost technological leadership. The relaxation of antitrust laws allowed greater monopolistic power not only through corporate combinations, but also through the multiplication of cooperation agreements (or legal cartel agreements) between firms. The extension of IPR to academic research and the intensification of its enforcement in a way that served dominant firms increased their monopolistic power. These regulatory transformations were first implemented in the United States but other developed countries also quickly followed the "American model". In the case of developing countries, the story of TRIPs showed how they were required, under the threat of trade sanctions, to embrace the pro-IP agenda. The story also shows how dominant firms were themselves behind the regulatory transformations put forth by the United States. The state, in this case, acted simply as an instrument serving the interest of private actors. While this whole regulatory transformation was implemented in order to encourage R&D investments and innovation, the result has been the emergence of the "me-too" business model, in which financial incentives discourage truly innovative research.

Dominant pharmaceutical firms might continue to lobby for greater IPR extension and other forms of privileges in the name of future innovation, the result is that such extension, in the actual system, simply discourages innovation. In the case of pharmaceuticals, the

contention of a knowledge-based economy allowing permanent innovation is a false idea. The accumulation regime in place increases profits while decreasing innovation. Nevertheless, the "me-too" business model cannot work in the long run if it is only based on a generous patent system. If this accumulation regime has succeeded until now, it is also because Big Pharma managed to extend its control by influencing physicians' prescribing behaviors, and its expertise in that field cannot be easily overstated.

7. PUSHING PILLS: THE MICROPHYSICS OF BIG PHARMA'S POWER

Let advertisers spend the same amount of money improving
their product that they do on advertising
and they wouldn't have to advertise it.
- Will Rogers

The medical profession is at the center of the pharmaceutical knowledge structure. While pharmaceutical firms supply products, physicians that prescribe drugs are the demand side of the sector. Normally, the purpose of prescribing physicians is to obtain the best health results and well-being for their patients. Except in rare cases, the physician does not have a budget constraint and his/her prescribing behavior is only marginally influenced by the price of the products. This inelastic demand enhances the fortunes of pharmaceutical firms, but they first have to convince doctors that their products are the best for their patients. Dominant firms can restrain competition all they want, but their business strategies are doomed to failure if they cannot bring doctors to prescribe their products. The possibility of the me-too business model in the pharmaceutical business exists because pharmaceutical firms managed to develop important influence and control over the medical profession through different promotional activities. While this dissertation has already introduced different elements to explain the increasing power of dominant pharmaceutical firms and their growing differential depth, the most decisive element is the influence developed by pharmaceutical firms over the medical profession. Promotion is the missing link that unites all elements of breadth and depth into a workable and durable regime of accumulation for Big Pharma.

Understanding the corporate forms of influence, control and power over the medical profession requires an in-depth analysis of the dealings between Big Pharma and the prescribing physicians. In order to do so, it is necessary to measure the exact amount of resources devoted to influencing prescribing behavior, followed by an analysis of the ways in which those resources are spent. This chapter first assesses the cost structure of pharmaceutical firms and then provides the most accurate possible estimate of the resources spent in the promotion of pharmaceutical products. It goes on to examine qualitatively the ways in which promotion results in the modification of the physicians' prescribing behaviors.

7.1 The Cost Structure of Big Pharma

Promotion is not a secondary feature of the GPB, it is its core competency. Marketing and distribution capabilities explain, in part, Big Pharma's dominance over the market, since a newcomer simply cannot access the same distribution facilities. However, spending in promotion is rarely publicized and it is difficult to obtain solid empirical data on the subject. Annual reports of Big Pharma firms, offer only a rough idea of the situation (table 7.1).

Table 7.1: Cost Structures for Big Pharma in 2006
(Billion $, 2006 Exchange Rates)

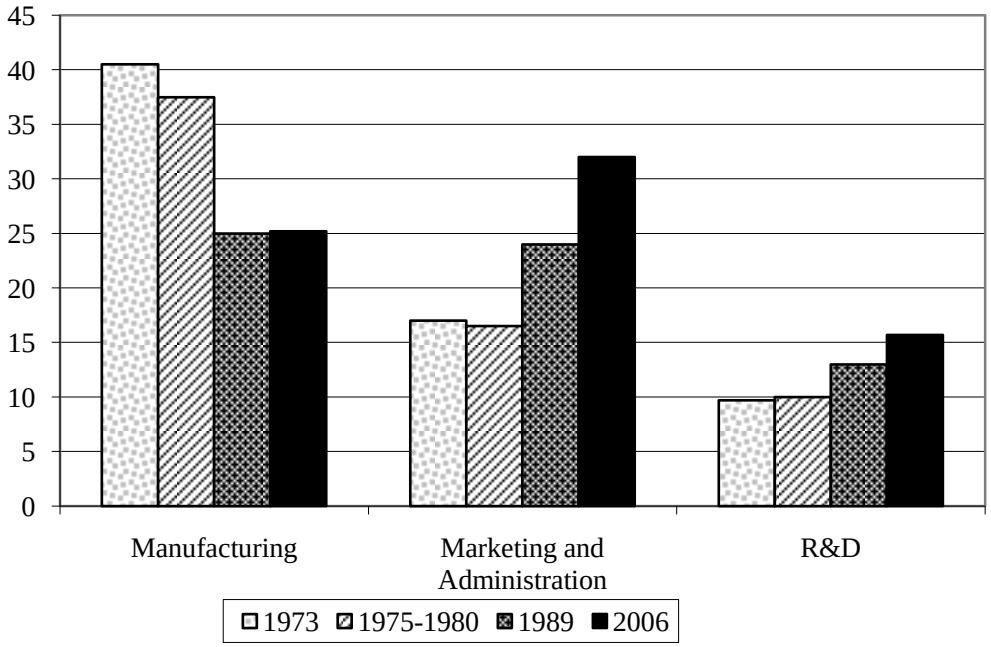
Firms*	Revenues	Manufacturing	Marketing & Administration	R&D
Abbott Laboratories	22.5	9.8	6.3	2.3
Amgen	14.3	2.1	3.7	3.4
AstraZeneca	26.5	5.6	9.3	3.9
Bristol-Myers Squibb	17.9	6.0	6.3	3.1
Eli Lilly	15.7	3.5	4.9	3.1
GlaxoSmithKline	43	9.3	13.5	6.5
Johnson & Johnson	53.3	15.1	17.4	7.7
Merck	22.6	6	8.2	4.8
Novartis	36	10.3	11.4	5.3
Pfizer	48.4	7.6	15.6	7.6
Roche Group	32	7.4	9.4	4.6
Sanofi-Aventis	36.9	9.5	10	5.5
Schering-Plough	12	3.7	4.7	2.1
Takeda	10.4	2.4	4.5	1.5
Wyeth	20.4	5.6	6.5	3.1
TOTAL	**411.9**	**103.9**	**131.7**	**64.5**
% of Revenues	**100**	**25.2**	**32**	**15.7**

*: Bayer was excluded from the list since pharmaceuticals represent only a third of its activities.

Source: Firms' Annual Report 2006, Source OECD.

Annual reports show that, in 2006, the revenues of 15 of the 16 Big Pharma firms were $448.2 billion. They spent $141.8 billion in marketing and administration and $67.4 billion in R&D. Marketing and administration represents 31.6% of revenues and 210% of their spending in R&D. In spite of different attempts at contacting firms directly, it was not possible to obtain meaningful disaggregated data. However, based on the large categories offered in annual reports, it is possible to obtain a rough picture of the evolution in the cost structures of Big Pharma. For example, UNIDO (Ballance et al. 1992, 123) gathered data for a sample of dominant research-oriented pharmaceutical firms until 1989. The comparison with the cost structure in 2006 provides an outlook into the transformation of Big Pharma (Figure 7.1).

Figure 7.1: Changing Cost Structure in Dominant Pharmaceutical Firms
(1973, 1975-1980, 1989 & 2006; % of sales)



Source: Ballance et al. (1992), Firms' Annual Reports 2006

The trends are clear. According to the OECD (2001b, 30-31): "Marketing expenditures show no sign of decreasing. Marketing expenditures (as a proportion of sales) rose sharply in the period 1973-1989, with profits (as a proportion of sales) rising over the same period". Between 1980 and 2006, manufacturing costs plunged by 12 points while R&D costs increased only by 6 points. Marketing and administration costs rocketed by 16 points.

Can we simply assert from those numbers that Big Pharma now focuses on promotion instead of research and development? Such assertion can be tricky on different grounds:

> 1) "Pharmaceutical" firms do not produce only pharmaceuticals. They can be diversified and it is not always possible to account only for their pharmaceutical divisions. The increase in marketing and administration might be caused by activities other than those in the pharmaceutical division.
>
> 2) The category "Marketing and administration", sometimes called "Selling and general" in annual reports, does not allow for the identification of how much is spent specifically in marketing or in administration.
>
> 3) "Marketing" remains a large category since it normally includes costs of promotion and advertising, but also cost of distribution such as transport and packaging.

Another problem is that official numbers of pharmaceutical promotion in the U.S., provided by the marketing research company IMS, contradict the idea of a promotional deluge. For example, based on the numbers provided by IMS, the lobby group PhRMA contends that pharmaceutical firms spend more on research and development (R&D) than on marketing. Using the same numbers, the U.S. General Accounting Office also claims that

"pharmaceutical companies spend more on research and development initiatives than on all drug promotional activities." (GAO 2002, 3). The rest of this section aims to show how central promotion has become in the accumulation regime of pharmaceuticals since the 1980s. In order to establish such an assertion, it is necessary to further analyze the level of pharmaceutical promotion in the United States by providing the most accurate estimate possible about firms' promotional expenditures.

7.2 The Cost of Pushing Pills: A New Estimate[72]

Pharmaceutical promotion can take various forms. Journal advertising and Direct-to-Consumer-Advertising are usually the most visible form of promotion for the population in general. The bulk of pharmaceutical promotion, however, is the systematic visit by sales representatives to physicians, but also to pharmacists, nurses and interns. Sales reps leave behind samples of their products, which are another form of promotion (even if the cost of samples is usually reported in the manufacturing costs of companies instead of the category "Marketing and Administration"). Other forms of promotion include the organization of promotional meetings where doctors are invited and sometimes paid to attend conferences about new products. Phase IV clinical trials are also sometimes used as promotional devices (seeding trials) in order to induce prescribing habits in doctors.

[72] The results of the research made by the author for this section have been published in the journal *PLoS Medicine* (Gagnon and Lexchin 2008). The author would like to thank particularly Joel Lexchin for his help and keenness on the subject.

Measuring Promotion

To measure with the most accuracy the level of pharmaceutical promotion, one cannot rely on the fuzziness of firms' annual reports. Two marketing research firms, however, provide data specifically on pharmaceutical promotion for the United States: IMS and CAM (now CSD). The two firms were contacted by the author to obtain more details about their methodology for calculating the cost of each category of pharmaceutical promotion in order to identify the most accurate number for each category. IMS and CAM are both private marketing research companies selling private data to pharmaceutical firms in order to help them organize their "marketing mix". The main difference between the two firms is that IMS monitors sales from firms and surveys firms to complete its data, while CAM collects its data by surveying doctors. CAM offers data on more promotional categories.

According to its website (www.imshealth.com), IMS provides business intelligence and strategic consulting services for the pharmaceutical and healthcare industries. It is a global company established in more than 100 countries. IMS gather data from 29,000 data suppliers at 225,000 supplier sites worldwide. It monitors 75 percent of prescription drug sales in over 100 countries, and 90 percent of U.S. sales. It tracks more than one million products from more than 3,000 active drug manufacturers.

According to its website (http://csd.cam-group.com/), CAM is a global audited promotional data company and is established in 36 countries worldwide. Media channels covered in the CAM Audit include: Detailing, Journal Advertising, Sampling, Direct Mail, Meetings, Clinical Trials, E-Activities and DTC promotion. Data targets include: Primary Care Physicians, Specialists and Pharmacists. To ensure the representativeness of its samples of doctors, CAM surveys each year 2000 Primary Care Physicians, and 4800 specialists in

different categories and in representative parts of the United States. Note that CAM merged with Cegedim in 2007 and is now called CSD (Cegedim Strategic Data).

Data for 2004, latest year for which data were available for both organizations, were obtained through the websites of the firms[73], but some private data were sent to the author directly by e-mail. Complete data were available only for the United States. While one cannot be sure that promotion expenditures in the United States reflects the reality in other countries, market shares in sales and promotion between the U.S. and the rest of the world seem to match. CAM calculated that in 2004 North America represented 44.4% of all global pharmaceutical marketing expenditures while, according to IMS, North America represented 44.1% of all global pharmaceutical sales.

The firms provided exact methods about how they collect data in each category and, based on the answers received, it was possible to select the most accurate figure for each category. CAM and IMS were both asked about the estimated value of unmonitored promotional expenditures. IMS did not provide an answer to this question. As for CAM, in order to validate its estimates, it relies on a validation committee that includes representatives from various pharmaceutical firms, including Merck, Pfizer, Bristol-Myers Squibb, Eli Lilly, Aventis, Sanofi-Synthelabo, AstraZeneca and Wyeth. Under a confidentiality agreement, firms supply CAM with internal data related to their promotional activities and costs in the United States. Through the validation committee, CAM can thus compare totals obtained through its own audits with the firms' internal data about their promotion budgets in order to evaluate if all promotion has been properly audited through its physician surveys. As a result

[73] Some of the data obtained online are now impossible to access directly but online copies of the originals are available at the following address: http://medicine.plosjournals.org/archive/1549-1676/5/1/supinfo/10.1371_journal.pmed.0050001.sd003.pdf

of this comparison CAM's validation committee considers that about 30% of promotional spending is not accounted for in its figures. While the official number cited by CAM for promotional expenditures in the United States in 2004 is $33.5 billion, its validation committee considers that this figure is thus short by 30% of the actual amount spent in promotion according to firms' internal documents. The results appear in Table 7.2.

Table 7.2: Promotional Spending on Prescription Drugs in the U.S., 2004
(According to IMS and CAM Group)

Type of Promotion	IMS (Billion $)	IMS % of Total	CAM Group (Billion $)	CAM Group % of Total
Samples	15.9	57.4%	6.3	13%
Sales Rep Contacts	7.3	26.4%	20.4	43%
DTCA (Data from CMR)	4	14.4%	4	8%
Meetings	—	—	2	4%
E-Promotion, mailing, clinical trials	—	—	0.3	0.5%
Journal Advertising	0.5	1.8%	0.5	1%
Unmonitored marketing (estimate*)	—	—	14.4	30%
Total	**27.7**	**100%**	**47.9**	**100%**

*: While this proportion does not appear in CAM reports, a CAM supervisory committee is able to establish this proportion of unmonitored marketing by accessing firms' internal documents. CAM is not allowed, however, to divulgate the details of those internal documents.

Source: Author's calculations based on numbers provided by CAM and IMS

Note that both IMS and CAM Group account for DTCA using the data provided by CMR, another market research company, and they also arrive at the same total for advertising

in journals. DTCA is usually legal for OTC drugs but forbidden for prescription drugs in most OECD countries, with the exception of the United States and New Zealand[74]. In the United States, prohibitions against broadcast forms of DTCA were relaxed in 1997 allowing a surge in television advertising; from 1996 to 2004 DTCA expenditures grew from $791 million (NIHCM 2001) to $4,024 million, according to CMR. Important differences appear, however, in other categories.

Because of the problematic nature of some data from each firm, the most precise picture of industry spending can be obtained only by selectively using both sets of figures. The first major discrepancy between the two sets of data concerns the value of samples. CAM estimates the amount spent on samples by multiplying the number of samples declared by physicians with their wholesale value. The latter is determined by using the average wholesale price, which is the amount set by manufacturers and used by Medicare in the U.S. to determine reimbursement. CAM then divides that amount in half to account for the fact that samples are frequently given out in small dosage forms. CAM admits, however, that its figure for samples is simply understated because, when physicians fill out the survey, any quantity of samples of the same product left during a visit from a sales rep is considered to be only one sample unit (this discrepancy is not part of the 30% gap with firms' internal documents since the costs of samples are reported in the manufacturing budget). Moreover, the average wholesale price has come in for extensive criticism since it does not account for the various discounts and rebates that are negotiated between manufacturers and purchasers (Gencarelli 2005). IMS, alternatively, provides exact figures for the retail value of samples

[74] In Canada, DTCA is partly forbidden: a firm can advertise about the need to see a doctor to treat a health problem (for example erectile dysfunction) but without referring to products treating the problem. A firm can also advertise the name of a product without referring to the effects of the product (for example *Viagra*) but it cannot advertise a product with a description of its effects.

by monitoring 90% of all pharmaceutical transactions and by tracking products directly from manufacturers. The IMS method for calculating the value of samples ($15.9 billion) is much more direct and therefore is likely to be subject to less error. Also, another reason why retail value should be favored over wholesale value is that drug companies themselves report the value of their drug donations in terms of retail value, instead of wholesale value (for example, PhRMA 2005) and the retail value of samples provided by IMS has been for a long time considered the official value of samples (for example, GAO 2002, 3). In the case of samples, the IMS figure is thus the most accurate figure available.

In the case of detailing, an important discrepancy appears between the two sets of data. IMS includes in the cost of detailing only the "cost to field the rep" (salary and benefits of the rep and the transportation cost). CAM offers more complete data since it includes in the average cost of a call (a sales rep visit to a physician) the "cost to field the rep" but also costs for the area and regional managers, costs of the training and detail aids such as brochures and advertising material. Furthermore, CAM relies on physician generated data to estimate the amount spent on detailing and is likely to give a more accurate figure than using figures generated by surveying firms. Companies may not report some types of detailing, for example the use of sales reps for illegal off-label promotion whereas doctors are not likely to distinguish between on and off-label promotion and would report all encounters with sales representatives.

In the case of unmonitored promotion, CAM is unable to provide an exact breakdown for this category. It believes, however, that around 10% is due to incomplete disclosure and omissions by surveyed physicians (due to the high number of visits by sales representatives, MDs can sometimes forget to declare some in the surveys) and the remaining 20% comes

from a combination of promotion directed at categories of physicians that are not surveyed (e.g. pediatricians), unmonitored journals in which pharmaceutical promotion appears, and unethical forms of promotion (bribes, lures, gifts, discounts, etc.). In fact, it is considered that the bulk of the remaining 20% is due to informal marketing practices, marketing done under the table. However, since this type of promotion remains undisclosed, hidden away in financial statements or even disguised as R&D, it is impossible to have an exact assessment of the importance of those practices.

CAM also obtained data for meetings and other forms of promotion such as e-promotion, mailing and clinical trials. Selecting the most relevant data for each category, it is possible to sum up the amounts spent in pharmaceutical promotion (Table 7.3).

Table 7.3: A New Estimate: Pharmaceutical Promotional Spending in the United States in 2004

Type of Promotion	Billion $	% of Total
Retail Value of Samples (IMS)	15.9	27.7%
Sales Rep Contacts (CAM)	20.4	35.5%
DTCA (CMR)	4	7%
Meetings (CAM)	2	3.5%
E-Promotion, mailing, clinical trials (CAM)	0.3	0.5%
Journal Advertising (IMS and CAM)	0.5	0.9%
Undisclosed marketing (CAM)	14.4	25%
Total	**57.5**	**100%**

Source: IMS, CAM, CMR

Interpreting the Numbers

It is thus estimated that, in 2004, $57.5 billion was spent on pharmaceutical promotion in the United States alone. From the data gathered here, $53.5 billion specifically targeted health professionals, and $4 billion targeted consumers directly. According to CAM disaggregated data obtained for Canada, only around 19% of all marketing was spent on pharmacists, nurses and interns. If the same proportion holds for the United States, then it can be argued that around $46 billion was spent on pharmaceutical promotion towards independently practicing physicians. With 700 000 practicing physicians in the U.S. in 2004 according to the OECD Health Database, then it is possible to assert that the industry spent on average $61 000 in promotion per practicing physician. As a percentage of U.S. domestic sales of $235.4 billion, promotion consumes 24.4% of sales, versus 13.4% for R&D[75].

This amount is comparable to that spent by firms specializing in brand management. For example, Pepsico, a brand management firm with products such as *Pepsi*, *Tropicana*, *Lays*, *Doritos*, *Aquafina* and *Quaker*, spent 23.5% of its sales in promotion for its products in 2004[76]. In terms of DTCA, which remains a very small part of their promotional campaigns, drug firms spend often more than brand management firms in order to promote their products. According to a study by NIHCM (2001) on prescription drugs and mass media advertising, each of the top seven most heavily advertised drugs beat Nike's ad budget. In

[75] According to rough calculations on the erroneous declaration of phase IV clinical trials as R&D instead of promotion (see below). Taking into account this fact would mean to transfer 1.5 points from R&D to promotion.

[76] Calculations based on Pepsico annual report 2004. Pepsico provides details about its advertising. With net revenues of $29.3 billion in 2004, Pepsico spent $1.84 billion in advertising (including deferred advertising) but also provided sales incentives of $6.6 billion accounted as a reduction of revenues. In order to calculate the ratio promotion to sales, $6.6 billion were added to net revenues, for a total of $35.86 billion in sales and $8.44 billion in promotion.

2000, $125 million was spent to advertise Pepsi Cola, $146 million on Budweiser beer, $169 million on GM's Saturn, $160 million on the top brands of Dell computers and $160 million on advertising for Vioxx alone.

In the literature, one can find many calculations of the ratio of promotion over sales using different methods based on extrapolations of firms' data for firms that are both transnational and diversified (Ballance et al. 1992, 123; OTA 1993, 90; Families USA 2002; CMS 2003, 28; Lauzon and Hasbani 2006; Consumers International 2006, 20). The importance of the new estimate provided here, however, is that it is based on quantifiable data from highly reliable sources and concerns only the promotion of pharmaceutical products in the United States.

It is not possible, however, to obtain such exact data in a historical perspective, but it is possible to clearly identify that there was a very important surge in promotional activities in the last two decades. DTCA increased by 509% between 1996 and 2004 (NIHCM 2001; CMR data). While the number of office-based physicians increased by 38% between 1996 and 2004, the number of promotional meetings increased in the same period by 254%, from 151 434 in 1996 to 536 734 (cited in Dougherty 2005). The number of sales reps went from 40,600 in 1996 to 101,500 in 2004, an increase of 150%, and the top 10% high-prescribing physicians received three to five times as many details in 2004 than they did 1990 (cited in Dougherty 2005). The corporate sponsorship of continuing medical education (CME) is also a derived form of promotion (not included in the previous analysis) since it provides indirect influence on the content of the CME courses (Kassirer 2005, 91-94). According to the Accreditation Council for Continuing Medical Education, commercial funding for CME went

from $188.8 million in 1996, which accounted for 29% of all CME revenue, to $1066 million in 2004, which then accounted for 52% of all CME revenue.

These recent numbers on the evolution of pharmaceutical promotion correspond to the changing cost structure of Big Pharma (Figure 7.1). The surge in promotion is a central feature of the recent evolution of the GPB. The recent differential profits of the GPB are not only linked with a trend of decreasing innovation, but also with a trend of growing promotion. The "intangible assets" developed by the firms have thus less to do with their increased productive capacities through immaterial means than their growing influence over the medical profession.

7.3 Impacts on Health and Research: Microphysics of Corporate Power

In Chapter 2, it was shown how the Veblenian institutionalist analytical framework can be helpful in analyzing capitalism. Institutions are defined as prevalent social rules and habits of thought that structure social interactions, and institutions are the embodiment of social power. They are not only a set of constraints, but also the configuration of possible actions as it weaves human possibilities with social control. Using a terminology focusing more on power than on institutions, the works of Michel Foucault complete the Veblenian approach to analyzing the nature of the social power of institutions. While the concept of power put forth by Foucault has been significantly criticized in academic circles for the way it impedes a clear understanding of the sources of domination, one should keep in mind that this was not the purpose of Foucault's works. Foucault analyzed the "how" of power, and not the "why".

As Rodney Loeppky explains (2005, 150-3), Foucault's exploration of *how* power relations take hold is especially relevant to understanding how particular social institutions, architectures and discourses are redirected in a way that better serve a changing society, more and more organized to serve the interests of capital (dominant corporations). It is believed that the works of Foucault can provide a better understanding of the numbers showing the importance of pharmaceutical promotion.

While Foucault's theory of power can be found to different degrees in almost all of his works, it is in the first volume of his *Histoire de la Sexualité* (1976) that one can find the most comprehensive presentation. For Foucault (1976, 121-122, author's translation), power is an omnipresent reality embedded in social structures:

> [By power, it] seems to me that first what needs to be understood is the multiplicity of relations of force that are immanent to the domain wherein they are exercised, and that are constitutive of its organization; the game that through incessant struggle and confrontation transforms them, reinforces them, inverts them; the supports these relations of force find in each other, so as to form a chain or system, or, at the contrary, the gaps, the contradictions that isolate them from each other; finally, the strategies in which they take effect, and whose general pattern or institutional crystallization becomes embodied in the mechanisms of the State, in the formulation of the law, in social hegemonies.

For Foucault, we must not seek a focal point of power from where we would derive everything else; power is produced at every instant in every social interaction. Power is everywhere; not because it is a totalitarian structure that includes everything, but because it comes from everywhere. Power is not a social institution, all institutions and social structures sweat power at every pore. Power is not a superstructure, it comes from the bottom. It is not imposed from the top; it is rather the multiple power relations in all social institutions that can be used to support larger possibilities for structural domination (1976, 124). What

Foucault calls the "microphysics of power" can thus be mobilized institutionally in order to create transverse divides in a number of local struggles to support greater structural domination. For example, Foucault analyzes at length biopower – the subjection of bodies and population control through various techniques, disciplines and normalizing machines – that has been a crucial element to the development of capitalism (1976, 185). Biopower explains, in part, for Foucault, the administration of the population for the needs of capitalist production in general, and it also explains the "differential distribution of profit" (1976, 186). Differential profitability, for him, should thus be explained from the bottom, from local power struggles, not from a central architecture of domination.

It was shown with Veblen that corporations are capitalized according to their present putative earning-capacity based on any of their institutional power that can translate into earnings. Their earning-capacity is the consequence of their structural power. However, following Foucault, it must now be considered that this structural power is not based on a central architecture of domination but, instead, on the mobilization and the shaping of multiple local struggles, or, as Foucault would put it, on transverse divides that crisscross a multitude of power struggles. Dominant corporations, or the dominant groups that own corporations, should be considered the social agents capable of producing grand strategies to mobilize social power in every possible interstice of the knowledge structure, in order to develop intangible assets and differential advantages. Remember that, for Veblen (1996 [1904], 142-143), "the substantial foundation of the industrial corporation is its immaterial assets", namely its capacity to gain an assured footing on some "immaterial" ground. With a Foucauldian twist, the dominant corporation can be understood as dominant only through its

institutional capacity to mobilize social power throughout the multiplicity of existing relations of force.

From such a point of view, competition between corporations should take the form of a competition to influence and transform social structures in order to mobilize social power to accrue differential earning-capacity. Here, we find ourselves at the centre of what is meant by structural competition: a competition to transform social structures, to create transverse divides in a multitude of power loci in ways that will translate into greater flows of earnings. Competition becomes structural by willingly transforming the socio-economic institutional settings to increase strategic control over industry and society by business interests. Dominant groups mobilize all their capacities and business network power to influence consumers, laws, policies, sense of nationhood, regulatory regimes, in ways to modify the socio-economic structure, so as to accrue their differential gains.

In the case of pharmaceuticals, the capitalist power struggles for differential accumulation can be found, for example, in the struggles to implement new health standards, to create new products, to get greater tax credits, to extend protection over patents, to produce sympathetic analysis of the industry, to modify doctors' prescribing habits, to influence consumers by advertising a better life through medication, to educate medical doctors or to commodify academic knowledge. However, as was shown, physicians are the main lucrative target in the medical knowledge structure since they embody the demand in this sector without having a budget constraint. Influencing doctors becomes one of the main features of structural competition.

The structural competition for differential accumulation must be analyzed from the local struggles that it creates to defend specific vested interests. The difference with Foucault is

that we need to consider that existing vested interests are huge organizations that managed to deploy vast control strategies over their industry. The difference between corporate capitalism and other forms of capitalism is there are organized going-concerns involved in every dimension of their sector that have developed an expertise in every aspect of the knowledge structure. For example, PhRMA not only undertakes traditional lobbying for favorable legislation, it promotes its interests through local struggles. It should not be surprising, for example, to learn that PhRMA pays a task force of economists to systematically refute any studies unfavorable to their interests[77], or that they paid writers for a thriller book, in which Serbian terrorists use the Canadian internet system of drug selling to mass-poison Americans, in order to discredit Canadian internet sales[78]. Little things can have enormous impact. Some lobbying is less a question of profit than a question of "principle": future earnings must be secured through the establishment of strict legal frameworks, since any little "exception" can be dangerous for the whole system; it is a threat to the general business model. Dominant firms do not only produce manufactured goods, they also produce the language and culture concerning their products and their industrial sector. The struggle for market shares is a struggle for the minds of physicians, patients and regulators.

Pharmaceutical firms struggle to transform the prescribing habits of doctors to increase their market shares and this struggle is undertaken in every interstice of the medical profession. The rising importance of promotion must be understood from that perspective:

[77] PhRMA spent $1 million in 2003-2004 for an "intellectual echo chamber of economists — a standing network of economists and thought leaders to speak against federal price control regulations through articles and testimony, and to serve as a rapid response team" (quoted in Pear 2003).

[78] The book called *The Karasik Conspiracy* (Spivak and Chrystyn 2006), was commissioned by a PhRMA employee in 2005. A few months after the book was rejected for being poorly written and not being sufficiently pro-Big Pharma, the authors decided to change the storyline completely and it is finally American pharmaceutical companies that poison Canadian-sourced drugs in order to stop their low-price selling to Americans (Sarasohn 2005).

promotion has become the most efficient way to increase corporate control over the pharmaceutical industry, the medical profession and the community at large. The huge promotional campaigns have become central for shaping the medical structures by deploying strategies, or transverse divides, that crisscross and mobilize a multitude of power struggles in order to enhance private earning-capacities.

The exhaustive inventory of all microstrategies deployed by firms in the microphysics of power in the medical profession would be simply impossible. For example, an extensive literature exists on the conflict of interest posed by multi-faceted interactions between drug companies and physicians.[79] Using some examples, however, is enough to approximate the landscape of corporate power in the medical knowledge structure. By keeping in mind that American pharmaceutical firms spent $4 billion in DTCA and an average of $61 000 in promotion campaigns per practicing physician in 2004, we can turn to specific examples. The reader must also keep in mind that, thanks to information collected by IMS on prescriptions, drug companies have at their disposal complete profiles of the prescription-behavior for each and every physician, which allows them to deploy much more efficient individually-targeted strategies. The section below highlights four different examples of corporate influence in the microphysics of power in relation to the medical profession: key opinion leaders, seeding trials, gifts and ghostwriting.

[79] On the different aspects of the corporate control over the medical profession, see for example Wazana (2000), Pignarre (2001), Lexchin & al. (2003), Krimsky (2003) Angell (2004), Healy (2004), Goozner (2004), St-Onge (2004), Moynihan and Cassels (2005), Van Duppen (2005), Kassirer (2005), Loeppky (2005), Abramson (2005), Prescrire (2008) and Petersen (2008).

Key Opinion Leaders

Some doctors are very suspicious towards drug reps, but can listen carefully to what other doctors have to say. For that reason, drug companies rely more and more on doctors to give "educational" speeches to other doctors about their latest drugs. In 2004, 237 000 meetings and talks sponsored by drug companies featured doctors as speakers, while only 134 000 were led by sales rep (Hensley and Martinez 2005). In fact, drug companies pay dearly to have key opinion leaders (KOL), doctors respected by other doctors, give a "scientific speech" at "educational events". KOLs receive an average fee of more than $3000 per speech from drug companies, usually using slides provided by the company (Moynihan 2008, 1402). In order for those scientific speakers to look independent, the company sometimes pays the fee to an academic centre, which then pays the KOL. Melody Petersen explains the practice by summarizing the story of a whistleblower in the case of Neurontin, a mediocre drug described as a miracle drug by KOLs:

> "The company got doctors to prescribe the drug for all these experimental uses by paying them. They paid physicians to give speeches to other physicians at restaurants or hotels or resorts. The doctors not only enjoyed a nice meal or a weekend vacation, they often also received a $500 check for attending. The physicians giving lectures at these parties were often trained by the drug company's ad firm to describe how Neurontin could work for conditions like bipolar. … The company tracked the doctors' prescriptions before and after these dinners or weekend retreats. The executives saw how well it worked." (quoted in Weissman 2008)

KOLs may have the respect of their peers but they are managed in a way that makes them simple drug reps. Kimberly Elliott, an ex-sales rep for drug companies, explains: "KOL were salespeople for us, and we would routinely measure the return on our investment, by tracking prescriptions before and after their presentations. If that speaker didn't make the

impact the company was looking for, then you wouldn't invite them back" (quoted in Moynihan 2008, 1402). Moynihan explains (2008, 1403) that another important trick of the trade is to maintain central databases on KOL to keep track of their "return on investment". A good KOL, however, can be hired for more tasks than only giving speeches, and the return on investment becomes more important. Marcia Angell (2009) explains:

> These are the people who write textbooks and medical journal papers, issue practice guidelines (treatment recommendations), sit on FDA and other governmental advisory panels, head professional societies, and speak at the innumerable meetings and dinners that take place every year to teach clinicians about prescription drugs. Having KOLs […] on the payroll is worth every penny spent.

Seeding Trials

Another example of corporate influence in the medical profession is the Phase IV clinical trial, 73% of which are being run only for commercial purposes. Note that the spending for promotional clinical trials in Table 7.3 is clearly understated since such promotional devices are considered as R&D instead of promotion by most firms. In 2004, 13.2% of R&D expenditures by American pharmaceutical firms ($4.9 billion) were spent on phase IV clinical trials (PhRMA 2006). Based on the data of the top 20 companies, it was determined that 73% of these trials are managed solely by the commercial, as opposed to the clinical, division of the biopharmaceutical companies. The remaining 27% of phase IV clinical trials were set up jointly by the commercial and the clinical division of the firms, which suggests that the vast majority of these trials are done only for their promotional value (La Puma & Seltzer 2002, 11). Only some rare firms, like AstraZeneca (Epstein 2006, 145-146), declare some of their phase IV clinical trials to be promotional devices funded from the

firm's marketing budget. In a nutshell, evidence shows that for major companies (excepting AstraZeneca), around 86% of the R&D spending declared for phase IV clinical trials, which means 11.4% of all R&D spending, should be considered as marketing expenditures. Roughly, in the case of the United States it could increase the total amount spent in promotion by around $4 billion for 2004 (while reducing the amount spent in R&D).

Such seeding trials are effective to influence physicians' prescribing habits. La Puma & Seltzer explain (2002, 10): "The primary purpose of this type of post-marketing research is to familiarize physicians and patients with new drugs". For the authors, there are no doubts: "Post-marketing research has been shown to influence physicians' drug choice and formulary recommendation". Kessler and colleagues (1994) already described how post-marketing trials were an important technique for drug companies to promote "me-too" drugs in a crowded therapeutic class. The reasons for this influence are multi-faceted. There is undoubtedly a financial incentive for doctors to join clinical trials, but when a doctor participates in a clinical trial, he is also working at collecting information to better serve patients with a view towards medical progress. A trial is designed to collect data; it is scientific research at work and, thus, mobilizes the professional ethics of doctors and their desire for personal achievement as professionals. Doctors get personally involved and try to learn more about the drug they are prescribing, they become more familiar with the drug; and, after the trial, they continue to be more likely to prescribe this specific drug, to which they have developed an affinity. The study by Andersen & al. (2006, 2764) confirms "that physician involvement in clinical trials is a powerful tool for influencing company-specific drug preferences".

Gifts and Samples

Another example of corporate influence is the extensive use of gifts, small and large. Gifts are important tools in influencing prescriptions; from giving pens and free lunches to medical students or a trip in the Caribbean for "high-prescribing physicians" in exchange of them attending "educational" meetings. According to Melody Petersen, 94% of doctors took something of value from the drug companies (Weissman 2008). Nevertheless, gifts, by definition, bring gratitude. As Katz et al. (2003) put it:

> When a gift or gesture of any size is bestowed, it imposes on the recipient a sense of indebtedness. The obligation to directly reciprocate, whether or not the recipient is conscious of it, tends to influence behavior [...] Food, flattery and friendship are all powerful tools of persuasion, particular when combined.

The ongoing gift culture is well developed in the medical profession since, from the beginning of their studies in medicine, students evolve in an environment in which drug companies are everywhere and seem like the natural companions that can fund and help every student, providing free lunches and special support. On a personal note, I was invited in March 2008 to give a speech to medical students about drug promotion at Université de Montréal. Before my introduction, the organizers of the conference revealed the results of an informal survey made the week before in which medical students were asked about conflicts of interests between physicians and drug companies. The vast majority of the students did not consider that it was a conflict of interest to receive funding from drug companies to organize academic activities. The majority also considered there to be no ethical problems in receiving a trip to the Caribbean in exchange for attendance to promotional activities put on by drug

companies (although their code of ethics forbid such practice[80]). Driving home the point, according to Wazana (2000, 373), a study found that 85% of medical students believe it is improper for politicians to accept a gift, whereas only 46% found it is improper for themselves to accept a gift of the same value from a drug company.

Drug reps surely know how to make the best use of this culture with the massive recourse to drug samples, the most widely used gifts given to physicians. Michael Oldani (2004), an anthropologist and former drug rep explains: "The importance of developing loyalty through gifting cannot be overstated [...] The essence of pharmaceutical gifting [...] is 'bribes that aren't considered bribes'." In fact, developing a friendship has become the on-going strategy for drug reps and they even have different scripts about how to build a friendship with a physician according to the physician's personality (Fugh-Berman and Ahari 2007). Such "friendship", however, serves only a commercial purpose, as the former drug rep Shahram Ahari (Fugh-Berman and Ahari 2007, 621) explains: "During training, I was told, when you're out to dinner with a doctor: 'The physician is eating with a friend. You are eating with a client'." Fugh-Berman summarizes the point: "Physicians are trained in medicine, not psychological manipulation. Every bit of flattery, friendship and information offered by reps is aimed at selling drugs" (quoted in Weissman 2008).

Well-established unofficial promotional practices exist throughout the entire medical profession. In the United States, when the Bush Administration announced its plan to curb rewards and bribes to doctors by implementing codes of conduct, drug companies fought

[80] In their *Guidelines for Physicians in Interactions with Industry* (available online: http://policybase.cma.ca/dbtw-wpd/Policypdf/PD08-01.pdf), the Canadian Medical Association leaves no ambiguity: "Practicing physicians should not accept personal gifts of any significant monetary or other value from industry. Physicians should be aware that acceptance of gifts of any value has been shown to have the potential to influence clinical decision making."

back by explaining to the government, in a public comment period, how important those practices were in the pharmaceutical sector. The *New York Times* journalist Robert Pear explains (2002):

> Drug makers acknowledged, for example, that they routinely made payments to insurance plans to increase the use of their products, to expand their market share, to be added to lists of recommended drugs or to reward doctors and pharmacists for switching patients from one brand of drug to another. Insurers, doctors and drug makers said such payments were so embedded in the structure of the health care industry that the Bush administration plan would be profoundly disruptive. [...] a coalition of 19 pharmaceutical companies, including Pfizer, Eli Lilly and Schering-Plough, said the Bush administration proposal was "not grounded in an understanding of industry practices." The payments and incentives to which the government objects are standard in the drug industry, they said. Merck & Company said it routinely gave discounts and payments to health plans to reward "shifts in market share" favoring its products. Merck complained that the administration proposal would "criminalize a wide range of commercial conduct" that the industry regards as normal and entirely proper.

A representative of Solvay Pharmaceuticals explained bluntly to the government how bribing doctors was in fact necessary for the good of patients/consumers: "We understand that bribes and other hidden remuneration should be prohibited. However, a policy statement that declares well-established commercial practices potentially criminal creates a chilling effect on commerce and ultimately harms all consumers" (quoted in Pear 2002). While the Bush Administration issued new guidelines on pharmaceutical marketing in April 2003, there are no signs that unethical forms of pharmaceutical promotion have decreased since then.

The situation is the same for pharmacists. In the Canadian province of Quebec, journalist André Noël investigated informal marketing practices by generic manufacturers, which usually target pharmacists[81] instead of physicians, aiming at making them switch from brand-

[81] Brand manufacturers usually aim only at physicians but they can sometimes aim their marketing at pharmacists. In the case of the United States, the OECD (2001b, 31) explains: "Drug companies have also sought to directly influence pharmacists, in some cases paying pharmacists to induce customers to change their drug consumption habits". As Levy (1999, 19) notes: "recent effort by brand-name drug companies have focused attention on ways to utilize pharmacists to enhance substitution rate among prescription drugs. The

name drugs to generics, or from one generic to another. In Canada in 2007, generic manufacturers with sales of $3.94 billion accounted for about 20% of the $19 billion worth of prescription medicines (CGPA 2008). While generic manufacturers have very low official marketing expenses, the investigation by Noël shows that 85% of pharmacists received gifts and discounts[82] from generic manufacturers – a practice forbidden by their professional code of ethics. The market of Canadian R_X generics was 1.88 billion in 2002 (CGPA 2008). An anonymous source contends that $0.5 billion was spent that year in gifts and discounts for pharmacists by generic manufacturers (Noël 2003a), which is consistent with the evaluation of the Quebec Order of Pharmacists that considers that gifts and discounts could represent as much as 28% of sales (Noël 2003b). This estimation could still be too low. Gifts and discounts could range anywhere between 35 and 50% of drug prices, reads one internal and confidential document that the daily Newspaper *La Presse* managed to obtain from a well-known manufacturer (Noël 2003b). While it is impossible to get an exact evaluation of hidden marketing expenditures for pharmacists, it represents, in this case, somewhere between 25% and 50% of the sales in generics.

Finally, samples are not only a type of gift used to "develop" relations with doctors, but they are also a clear promotional device for seeding treatments to patients. Drug companies and industrial lobby groups contend that samples are important since they are used as a safety net to provide treatments to poor and uninsured patients. A representative analysis of patients receiving drug samples in the U.S. shows, instead, that poor and uninsured Americans are less likely than wealthy or insured Americans to receive free drug samples (Cutrona et al.

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drug switch programs of brand-name drug companies, however, involve therapeutic substitution and not the substitution of generic for brand-name drugs".

[82] Most of the time gift certificates, cash, travels, home theater systems, computers, cars, usually undeclared for tax purposes (Noël 2003a).

2008). In fact, this can be explained by another study that shows that patients accepting free samples spend overall 40% more in out-of-pocket prescription costs than those not receiving samples (Alexander et al. 2008). The reasons are simple: A free sample gives the patient the opportunity to "try" a treatment, and if the treatment works the patient normally sticks to it and begins paying for it. Since promotional campaigns and distribution of samples are organized mostly for brand-name products under patent protection, the price of those treatments gets far more expensive than similar off-patent treatments. The distribution of free samples is organized with the aim that more wealthy patients will have the capacity to stick to the treatment after the free samples run out.

Ghostwriting and Hidden Studies

Another dimension of drug promotion directly affects research outcomes. Chapter 4 showed how RCTs are shaping the medical knowledge structure and can be steered in such a way that medical progress develops treatment niches with low benefits but high commercial potential. This is done on a systemic basis, in such a way that nobody is directly manipulated and everybody believes he is genuinely working in the best possible way towards medical progress. Sometimes, however, manipulation or embellishments of research results are made in a way that knowingly abuses physicians. It is well known that industry-sponsored research on a particular drug is much more likely to produce results in accordance with the interests of drug companies than research funded by any other source (Lexchin et al. 2003; Healy and Cattell 2003). Drug companies must normally mention that they sponsored the research when they publish the results, allowing physicians to compare such results with independent studies. However, drug companies often make use of ghostwriting, which means that they

pay doctors to put their names on studies sponsored by the company in order to make them appear independent. Very little data exist on such a practice since it is hidden by definition. Nevertheless, internal documents from Pfizer that were made public in a trial showed that 85 "scientific" articles on sertraline (the anti-depressant *Zoloft*) were written directly by a medical writing agency employed by Pfizer while the scientific literature counted at the time only 211 articles with sertraline in the title, and 479 articles with sertraline as a keyword. Those numbers suggest that between 18% and 40% of articles on sertraline in this key period were managed by Pfizer through this one agency (Sismondo 2007). Medical writing agencies, like contract research organizations, are firms that sell their services to pharmaceutical companies by developing the expertise to give the latter favorable results. Pfizer produced, in this way, a critical mass of articles that were favorable to the drug, thus allowing its drug reps to "drown out" any unfavorable studies. According to Petersen (2008, 189), in 2006, the medical writing agency Complete Healthcare Communications boasted that it had written more than 500 manuscripts for their pharmaceutical clients, 80% of which has been published in scientific medical journals.

The Vioxx scandal rests precisely on this premise. Jeffrey Lisse, a doctor who wrote a "scientific" article on Vioxx that "omitted" mentioning the death of some participants in the clinical study, told *New York Times*: "Merck designed the trial, paid for the trial, ran the trial [...] Merck came to me after the study was completed and said, 'We want your help to work on the paper'. The initial paper was written at Merck, and then it was sent to me for editing" (quoted in Berenson 2005a).

In other cases, drug companies can simply "omit" the publication of important studies. One study showed that the industry systematically failed to publish adverse studies about the

new generation of antidepressants, including Pfizer's *Zoloft* (Turner et al. 2008). On 74 clinical trials devoted to this new generation of antidepressant, 38 were favorable to the drug, but 36 considered the drug useless or questionable. 94% of the favorable studies were published, 23% of adverse studies were published, but two-thirds of published adverse studies were written in such a way (by medical writing agencies) to convince the reader of favorable results. When reading available studies, a physician could easily come to a biased opinion about the benefits of this new generation of drugs, which explains the great facility with which physicians began prescribing antidepressants on a systematic basis (Pignarre 2001; Healy 2004).

History repeats itself for cholesterol lowering agents like Vytorin and Zetia, manufactured jointly by Merck and Schering-Plough. There are more than a million prescriptions for those drugs every week. Adverse studies conducted by the manufacturers were hidden away since April 2006 and only made public by the manufacturers in January 2008 due to the threat of lawsuits. Studies clearly showed that, except for rare types of patients, the drugs had no impact whatsoever in reducing heart-attacks risks (Berenson 2008). In the meantime, the two companies continued to make billions out of this drug lacking in any benefit.

In these circumstances, one can only share the grim conclusions by Marcia Angell (2009), who served for two decades as an editor of *The New England Journal of Medicine*: "It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines".

These four examples do not summarize all the ways corporate influence is at work in the microphysics of medical knowledge and practice. Those do show, however, how extensively and efficiently such corporate strategies can influence doctors. Zoloft, Vioxx, Neurontin, Zetia or Vytorin are not exceptions, rather they are the most prominent examples of practice that is omnipresent in the medical profession. We have to consider that even conscientious independent physicians, free from any financial incentives and wanting only the best interest of their patients, can be seriously misled in the choice of their prescriptions because of the amount of biased information that exists on different drugs.

From this perspective, it is not very surprising to learn that general prescribing habits can be modified, even when the new products are less efficient than older (and cheaper) ones. For instance, Peter Jones et al. (2006) has demonstrated that schizophrenia patients treated with the first generation antipsychotics were in fact doing better than those treated with the second generation antipsychotics, which are the current standard prescriptions, and which cost ten times more than older antipsychotics. Describing why their colleagues embraced such prescribing habits, Jones suggested that: "*Duped* is not right", he said, "We were *beguiled*" (quoted in Vedantam 2006). A similar scenario had already developed for antihypertensive drugs: an important publicly-funded study showed that a new generation of antihypertensive drugs, which cost twenty times more than the earlier generation (diuretics), brought fewer therapeutic benefits than the older generation (ALLHAT 2002). When trying to understand the reasons behind a "decade of irrational prescribing" in antihypertensive drugs, Atle Fretheim (2003) arrived at the conclusion that opinion leaders played a major role in transforming prescribing habits, and that conflicts of interests between physicians and drug

companies remain largely unexamined. Six years after the publication of the results, prescribing habits for antihypertensive drugs have not changed (Pollack 2008):

> Pharmaceutical companies responded [to the Allhat 2002 study] by heavily marketing their own expensive hypertension drugs and, in some cases, paying speakers to publicly interpret the Allhat results in ways that made their products look better. "The pharmaceutical industry ganged up and attacked, discredited the findings," Dr. Furberg said. He eventually resigned in frustration as chairman of the study's steering committee, the expert group that continues to oversee analysis of data from the trial. One member of that committee received more than $200,000 from Pfizer, largely in speaking fees, the year after the Allhat results were released.

From all this, it is not unreasonable to assert that the GPB does not even need to produce anything beyond mild therapeutic innovation, since its capacity to influence drug consumption habits is such that it can thrive without it. Rising profits and declining innovation are possible only because the GPB has developed huge control over the medical knowledge structure. Pharmaceutical research becomes more beneficial to the GPB when it is managed as a marketing strategy, rather than as a process for therapeutic innovation. Elena Dusi (2008) synthesizes the point when she pronounces the tyranny of marketing responsible for "killing softly" pharmaceutical research. This general state of affairs is coming under increasing scrutiny, as we read more and more about drugs with unfulfilled promises and less about genuine breakthroughs. In the story on the first page of the influential newspaper, *Le Monde*, on January 3, 2008, it reads that drug companies themselves are searching for a new business model based on innovation, instead of promotion (Mamou 2008). In fact, drug companies would like the public image of life-saving researchers in white coats to replace the one of greedy drug reps. However, the actual business model based on low innovation and aggressive promotion remains a financial success, since it has created an accumulation

regime providing generous differential depth for Big Pharma. Systemically, there is no incentive to scuttle a business model that serves the interests of the shareholders, even if it is to the detriment of patients' health.

CONCLUSION: THE KNOWLEDGE-BASED ECONOMY REVISITED

The law locks up the man or woman
Who steals the goose from off the common
But leaves the greater villain loose
Who steals the common from off the goose.

The law demands that we atone
When we take things we do not own
But leaves the lords and ladies fine
Who take things that are yours and mine.

The poor and wretched don't escape
If they conspire the law to break;
This must be so but they endure
Those who conspire to make the law.

The law locks up the man or woman
Who steals the goose from off the common
And geese will still a common lack
Till they go and steal it back

-Anonymous, circa 1764

In October 2008, I attended a presentation at McGill University by a Commissioner of the Federal Trade Commission (the U.S. antitrust division) and other jurists about the difficult equilibrium between intellectual property rights and competition policies. The Commissar's speech, explaining the Court's decision in favor of Microsoft in the antitrust case concerning the bundling of software, was a long and passionate defense in favor of the business practices of Microsoft. It took some time to absorb the fact that the person speaking was representing the U.S. government and not Microsoft, but the speech proved to be of particular interest. The ultimate standard for any decision, the Commissar contended, was innovation. All decisions to be taken relied on one criterion: do the business practices involved bring more innovation (thus utility, thus welfare) to the community? During the

question period, this author posed a simple question: “If more innovation is the ultimate standard for any decision, then one needs to measure innovation in order to know if we have more or less innovation. How do you measure innovation?” The panelists were a little taken aback by this question, but I was even more taken aback by their answer: “Well, that’s the thing; it is not really possible to measure innovation in any conclusive way”.

In other words, any judicial and political decisions in favor of increasing innovation are, to a certain extent, arbitrarily based. Decisions can rely on profitability or the number of patents obtained, but it is not possible to assess innovation directly. Technology provides no standard to assess the validity of innovation in technical terms. Technological progress is not the accumulation of knowledge brick by brick towards universal knowledge; it is a process of cultural evolution that transforms constantly the ways and means and the know-how with which a community meets its material needs. The profits of capital in the KBE cannot be considered to be the counterpart of innovation, since innovation cannot be measured. Are profits in the KBE simply arbitrary? This dissertation contends that, on the contrary, one can consider the amount of profits to be related to the control exercised by firms, as going-concerns, over the community. Using the works of Veblen, it has been suggested that the more that cultural transformations made the community dependent on specific firms, the more intangible assets these firms develop, and the more profits can be generated.

The purpose of this dissertation has been to analyze the nature of capital in the knowledge-based economy (KBE). As compared to prevailing idealized views about a “New economy”, driven by the miracles of new technology, the institutionalist analysis used here provides a better understanding of the capitalist dimension of the KBE by identifying the institutional transformations that increase intangible assets and earning-capacities for

knowledge-based firms. The analytical framework of differential accumulation through structural competition, applied to the case of the global pharmaceutical business (GPB), offers unique insights into the nature and ramifications of capitalist power in a specific sector. While it is impossible to specify conclusions about other knowledge-based sectors, because of their different knowledge structures, the results obtained for the GPB offer many insights about the general nature of capital in the KBE, or in the economy in general. At least five general conclusions emerge from the analysis of the GPB in terms of differential accumulation.

First, the results obtained concerning the GPB show a clear-cut reverse relation between innovation and profits. With the capacity to measure therapeutic innovation in terms of quantity and quality of new molecular entities, the GPB shows that the differential increase in profits, absolute or ROR, for dominant pharmaceutical firms was paralleled with an important decrease in innovation. Even if those results cannot be extrapolated to other sectors without prior analysis, they do confirm that any analysis postulating an inherent link between profits and innovation, or between capital and productivity, are problematic. The analysis of the GPB shows how much the implicit link we find in standard economics between knowledge, productivity and profitability is broken. The results suggest, instead, that we can find a clear relation between control over the knowledge structure, power accumulation and profitability.

Second, analyzing the power structures in GPB allows identifying 16 dominant firms (Big Pharma) as the core organizations structuring the whole sector. The empirical findings show how important cooperation is between capitalist firms in this sector, bringing cooperation to the forefront of its capitalist dynamics, as compared to competition.

Competition is no driving engine of accumulation, since the sector is organized as a pseudo-cartel with very important barriers to entry, and showing no sign that it is weakening with time. The existing supporting nexus is most of the time totally dependent on dominant firms. Here, market competition is simply an elusive idea.

Third, transnational dominant firms are the main agents driving capital accumulation in this sector, as well as shaping the knowledge structure in pharmaceuticals, and states are highly conducive to the aims of transnational dominant firms. Once again, this dissertation does not aim at providing a general theory according to which states are mere instruments in the hands of firms; it simply argues that the state was highly responsive concerning the pharmaceutical sector. Indeed, the role of the state was central in developing the KBE. The KBE, understood quantitatively as the differential accumulation in knowledge-based sectors, was the product of an American strategy put forth by the Conservative Reagan Government in 1980 in order to regain lost world market shares and to restore American global leadership in technology. Relaxing antitrust laws, re-enforcing IPR nationally and imposing IPR standards abroad were key-drivers in the dynamics of capital accumulation for pharmaceuticals. Importantly, however, the analysis of the mechanisms of forum-shifting showed how state power was mobilized first and foremost by private actors, and that the state is better understood in the case of the GPB as secondary actor, instead of an effective counter-power.

Fourth, the analysis shows that, if market competition cannot be observed, the best way to understand capitalist competition is to focus on structural competition. This means assessing coalitions of private actors and how they shape and transform social structures and institutions. The increase in the profit margins of dominant pharmaceutical firms was

possible with the multiplication of privileges obtained through the state, such as the extension of IPR, tax credits, relaxed anti-monopoly regulation, increasing collaboration between firms, and increasing technology transfer from public organizations to private firms.

Note that if the capitalist dynamics in the GPB rest on cooperation, accumulation of privileges and institutional transformations of social structures, then the nature of capital accumulation for this sector becomes far different from standard definitions of capitalism in terms of competition and market imperative. Some may consider that such institutionalist analysis of the GPB is opening the door to theoretical debates about the nature of capitalism itself. Such a debate is not the goal for this dissertation. The results obtained for the GPB might be impossible to generalize to other sectors, but the existence of those results merit further investigation in relation to the overall dynamics of capitalism. The idea of structural competition observed in the pharmaceutical sector challenges accepted ideas of value creation. To put it in Marxist terms, if the realization of the value of products is determined socially through the system of needs, then the analysis of the GPB shows that the system of needs in pharmaceuticals is not an independent variable, but is itself produced by dominant firms through regulatory capture, massive promotion and the strategic orientation of research. Capitalist power of dominant firms is thus less the capacity to produce value than the institutional capacity to directly produce the social determinants of value.

Finally, the analysis of the GPB points to a new and original observation of the workings of power. While power in the GPB is usefully understood through Foucault's microphysics of power, Foucault himself did not believe that such power could be accumulated or captured — it was too diffuse for any actor to corral for his/her own purpose. By identifying dominant pharmaceutical firms, however, it is possible to identify specific actors with the capacity to

deploy grand strategies aimed at every crevice of the knowledge structure. As such, Foucault's microphysics is well suited to explain the "how" of power, but the size, expertise and monopolistic capacities of dominant corporate actors make them capable of capturing such diffuse power to their own ends.

Accumulating Power: the Case of the GPB

By analyzing the case of the GPB, the dissertation identifies the specific dynamics of a specific sector. The regime of capital/power accumulation allows positive differential accumulation for dominant pharmaceutical firms based on their growing control over the knowledge structure. This growing control of dominant firms can be broken down into four elements: 1) externalization of innovation costs to a supporting nexus (private and public), coupled with control over innovative compounds through entry barriers and the possibility of mergers and acquisitions; 2) increasing monopolistic capacities due to greater industrial concentration, mostly through mergers and acquisitions; 3) appropriation of the community's knowledge, extending IPR nationally and abroad through the capture of state regulations; and 4) massive promotion of products towards physicians in a manner that strengthens Big Pharma's hold over medical knowledge.

These dynamics have created a stable accumulation regime for this sector. A regime based on a generous patent system, which allows dominant interests to increase their control over every aspect of productive capacity, forces competitors and a supporting nexus of firms to cooperate with dominant firms. IPR render cartels effectively legal, and financial incentives for breakthrough innovation are, in fact, largely minimized. This is not to say that there has been no genuine therapeutic innovation since 1980, but it does mean that the

incentives are structurally disappearing for such innovation. The counterpart for the decline in innovation, however, has been the necessary extension of influence over medical practice, ensuring that new products, even when they do not significantly improve patients' health, can still become blockbusters. Pharmaceutical promotion not only increases demand for newer products with little incremental therapeutic value, it shapes and transforms medical knowledge according to the interests of dominant firms.

For many years, the decline in therapeutic innovation has been interpreted by many as the coming collapse of Big Pharma (Economist 2004; Alpert 2005; Mamou 2008). The detailed analysis of power structures at play in this sector shows, instead, that the accumulation regime at work has been decidedly successful, allowing growth in differential profits for Big Pharma. And as long as no policies emerge to reduce Big Pharma's control over the pharmaceutical knowledge structure, there is no reason why this accumulation regime would be altered or significantly diminished.

The nature of capital accumulation in the pharmaceutical sector can be interpreted not only as an increasing control of the pharmaceutical business over the pharmaceutical knowledge structure and the community at large, but also as an increasing dependence of the community on Big Pharma. The privatization of "knowledge commons" in the hands of dominant firms is a central feature of contemporary economic restructuring. While, here, the results focused on the GPB, the same dynamics seem to exist outside pharmaceuticals, for example, in the cases of food (Tansey and Rajotte 2008) or the environment (Robin 2008). It does not seem far-fetched to suggest that, in the last 30 years, corporate control over knowledge structures has been globally increasing by allowing, among others, the private appropriation of essential aspects of health, food, reproduction and environment. For

example, analyzing those dynamics, Drahos and Braithwaite arrive at a gloomy prediction (2002, 166-168):

> US support for big business regulatory agenda of ever longer, broader and stronger intellectual property rights for the global information economy risks a deepening of cartelism. The chemical and pharmaceutical oligopolies of the 20th century will, using intellectual property rights over biotechnological processes and products, progressively transform themselves into the biogopolies of the 21st. […]The dangers of biogopolies are not simply those that relate to prices and consumer welfare, although they are real enough. They run deeper. The globalization of intellectual property rights will rob much knowledge of its public good qualities. When knowledge becomes a private good to be traded in markets the demands of many, paradoxically, go unmet. […] Much of what happens in the agriculture and health sectors of developed and developing countries will end up depending on the bidding or charity of biogopolists as they make strategic commercial decisions on how to use their intellectual property rights.

For sure, we are not there yet, but the current dynamics are projecting us in that direction. For example, as a solution to the current innovation crisis in the pharmaceutical sector, drug manufacturers suggest that they need to invest more in the production of new breakthrough drugs, and, in order to do so, governments must lower taxes, increase IPR, speed up commercialization of public R&D and reduce the regulatory "burden". This dissertation shows that, because of the confusion between productivity and profitability, such policies should not be considered solutions to but, rather, as causes of the crisis in therapeutic innovation. The current business model of low innovation and massive promotion emerged from the increasing power offered to pharmaceutical firms, in order for them to extend their profitability. Looking at industrial policies proposed by public authorities in the U.S (Economic Report of the President 2006) or in Canada (Innovation in Canada 2007), it seems that states have embraced the agenda of reforms proposed by pharmaceutical firms, since national competitiveness in a specific sector is still measured only by the increasing profitability of national firms. A new agenda for reforms must be put forth.

It is not the topic of this dissertation to comment on the possibility of different reforms. Whatever the choice of the reforms, however, this dissertation has demonstrated that the problem must be put in terms of power, and the solution must also be configured in terms of power. As Montesquieu (1748 Book XI, Chapter IV, author's translation) aptly stated it in *L'esprit des Lois*: "To prevent abuse of power, it is necessary from the very nature of things that power opposes power." Differential accumulation by structural competition in the GPB will continue to the detriment of innovation and public health as long as no counterweight exists against dominant firms. Competition among firms is an elusive idea in an environment where the state acts in the interest of national firms and the medical profession remains subjected to the influence of these dominant interests.

By making explicit the productivity doctrine of capital that confuses productivity and profitability, this dissertation directly challenges the optimistic view that a KBE is driven by the miracles of new technology and necessarily benefits public welfare. By unpacking capitalist dynamics within the GPB, with recourse to the most reliable data about this sector, this dissertation has exposed the weaknesses of such grandiose claims. Bringing to light the mechanisms of differential accumulation in the pharmaceutical sector, this analysis can transform growing public anger at pharmaceutical firms into a sustained and systematic agenda for structural reforms.

APPENDICES

APPENDIX A - Measuring Big Pharma Differential Accumulation

To organize the figure, I collected all data provided by *Fortune* about profits made by the 500 most important U.S. firms in terms of revenues since 1954. For the purpose of this graph, I identify Big Pharma simply as pharmaceutical firms appearing in the *Fortune 500* list. In spite of those limits, the figure provides a good indication of the historical evolution of the differential accumulation in the pharmaceutical sector. Note that until 1993, *Fortune* included in its list only firms in mining and manufacturing, but opened the list to all firms in 1994 (including financial firms), which causes a bit of discrepancy in the data for all firms. In the case of pharmaceuticals, all firms defined as dominant remained in the new version of the list.

To measure the average profit for all firms, I added up all profits for all reported 500 firms in the *Fortune 500* each year, divided by all reported firms. *Fortune* defines "profits" as after-tax profit, after extraordinary credits or charges if any appear on the income statement, and after cumulative effects of accounting changes. Profits for real estate investment trusts can be slightly overstated since they are not taxed at the corporate level. Cooperatives are excluded from our calculations since they provide only net margin figures, which are not comparable to profit figures. Profits for mutual insurance companies are based on statutory accounting.

I measured the average profit for dominant U.S. pharmaceutical firms by adding up their profits and by dividing it by their number on the list. I took into account that some pharmaceutical firms produce not only pharmaceuticals, and that non-pharmaceutical firms can sometimes produce a lot of pharmaceuticals. I thus identified dominant pharmaceutical

firms not only with firms specifically categorized with pharmaceuticals, but also with firms that simply had an important part of their revenues made in the pharmaceutical sector. The purpose of those calculations, however, is to analyse the evolution of agents (firms) that will come to dominate the sector and not to analyse their degree of specialization in pharmaceuticals. Since some of the actual dominant firms had at first only a branch of their production devoted to pharmaceuticals, I chose to include them as soon as they produced a significant amount of pharmaceuticals. I identified below the different firms I considered in my analysis of differential accumulation in pharmaceuticals (Table A.1).

Fortune 500 Firms considered as dominant pharmaceutical firms

Firms included	Years	Comments
Abbott Laboratories	1954-2006	
Bristol-Myers-Squibb	1954-2006	
Eli Lilly	1954-2006	
Johnson and Johnson	1959-2006	Began significant production in pharmaceuticals in 1959 after buying McNeil Labs
Merck	1954-2006	
Pfizer	1954-2006	
Schering-Plough	1957-2006	
Wyeth	1954-2006	
American Cyanamid	1954-1993	Bought by American Home Products (Wyeth) in 1994
Sterling Drug	1954-1987	Bought in 1988 by Eastman-Kodak
Dart Industries	1954-1979	Merged with Kraft in 1980
Parke-Davis	1954-1969	Bought by Warner-Lambert in 1970
Squibb	1954-1988	Bought by Bristol-Myers in 1989
Richardson-Vicks	1954-1985	Bought by Procter & Gamble in 1985
U.S. Pharmaceuticals	1954-1988	U.S. division of Smithkline, disappears after Smithkline merged with Beecham in 1989

Warner-Lambert	1954-1999	Merged with Pfizer in 2000
Pharmacia	1958-2002	Becomes part of Monsanto in 2000-2001; Bought by Pfizer in 2003
Miles Laboratories	1958-1986	Bought by Bayer in 1978; Becomes Bayer U.S. headquarters in 1986
Mead-Johnson	1960-1967	Bought by Bristol-Myers in 1967
G.D. Searle	1967-1984	Bought by Monsanto in 1985
Monsanto	1985-2000	Began in pharmaceuticals after buying G.D. Searle in 1985; includes Pharmacia in 2000-2001
Rhone Poulenc Rorer	1983-1993	Rorer bought by Rhone-Poulenc in 1990; Considered a non-U.S. firm since 1994
Bayer Corporation	1986-1993	Considered a U.S. firm after establishing a U.S. headquarter in 1986; Considered a non-U.S. firm since 1994
Marion Laboratories	1987-1989	Merged in 1989 with Merrell-Dow Pharmaceuticals
Amgen	1999-2006	

Note that some firms producing pharmaceuticals are not included in the list for two reasons. First, I excluded from the list two large-sized firms, Eastman-Kodak and Dow Chemical, which began devoting a part of their production to pharmaceuticals by the end of the 1980s, but never managed to succeed in this sector (Chandler 2005). To include those two large firms in the analysis of the evolution of profits for pharmaceutical firms would have created an important bias in the data since the bulk of their profits were made in other sectors. It would have created an artificial surge in the average pharmaceutical profits from 1988 to 1995. Also, I excluded from the list three minor medium-sized firms that appeared in the *Fortune 500* between 1991 and 1993: Block Drug, Amgen and Du Pont Merk Pharmaceutical. Since the *Fortune 500* list included only mining and manufacturing firms until 1993 and becomes open for all firms in 1994, those minor medium-size firms that cannot in any way be considered dominant firms at the time, appear in the list mostly because

of artificial methodological circumstances. To include those firms would have created an important bias by lowering the average pharmaceutical profits for the years 1991 to 1993. Note that Amgen is reinstated in the *Fortune 500* in 1999, as it emerges as a new dominant firm in this sector. Note also that, according to the filtering, almost simultaneously, two firms that artificially increase and three that artificially decrease the average profits of pharmaceutical firms are excluded, balancing more or less the impacts of the exclusion (see Table A.2).

Table A.2

Pharmaceutical firms appearing in the Fortune 500 List, but excluded from our calculations

Firms Not Included	Years	Comments
Eastman-Kodak	1988-1994	Began production in pharmaceuticals in 1988 after buying Sterling Drug; Sold all pharma division in 1994
Dow Chemical	1990-1995	Began production of pharmaceuticals after buying Marion Labs in 1985; Sold all pharma divisions to Hoechst in 1995
Block Drug	1991-1993	Bought by GlaxoSmithKline in 2001
Amgen	1991-1993	Reappeared in the Fortune 500 list since 1999
Du Pont Merk Pharmaceutical	1991	Joint Venture between Dupont and Merck

While the choice of firms selected can remain the subject of heated debate, the chosen selection identifies well the dominant pharmaceutical firms that embodied “Big Pharma” in the United States since 1954.

APPENDIX B - Merck's On-Going Cooperation Agreements (2008)

Name	Products	Content of Agreement	Date
Actelion	blood-pressure medications	R&D and commercialization agreement	12/03
Acumen Pharmaceuticals Inc.	research and development of monoclonal antibody products, option to develop vaccine products and diagnostic products	exclusive licensing agreement, amended to grant Merck license to develop amyloid-derived diffusible ligand directed against diagnostic products (11/06)	1/04
Addex Pharmaceuticals AG	ADX63365	R&D collaboration	1/08
Advinus	candidates against metabolic disease targets provided by Merck	discovery and development collaboration	11/06
Agensys Inc.	Agensys' AGS-PSCA	licensing agreement	10/05
Alnylam Pharmaceuticals Inc.	RNAi technology research and RNAi-based therapeutics	R&D agreement	9/03
Ambrilla Biopharma Inc.	PPL-100	exclusive worldwide licensing agreement, Ambrilla to receive up-front licensing fee of $17M and up to $215M in milestones and future royalties	10/06
Ariadne Genomics Inc.	MedScan Text-to-Knowledge Suite software	licensing agreement	11/05
Artemis Pharmaceuticals GmbH	construction of of shRNAi, genetically engineered mouse models for the in vivo functional analysis of selected disease related genes	research agreement	11/06
Artemis Pharmaceuticals GmbH	construction of RNAi-modified genetically engineered mice	research services agreement	10/04
Avalon Pharmaceuticals Inc.	identification and development of inhibitors for an undisclosed target that is important in the development of cancer	drug discovery, development and commercialization collaboration	3/07
AVEO	use AVEO's Human Response	discovery and development	11/05

Pharmaceuticals Inc.	Prediction platform to identify populations likely to be responsive to Merck cancer drugs	agreement	
Benitec Ltd. and Promega Corp.	ddRNAi technology	worldwide nonexclusive licensing agreement	7/04
BioImage A/S	BioImage's Redistribution technology	licensing agreement	9/04
BioXell SpA	development of TREM-related therapeutic and diagnostic products	exclusive, worldwide licensing agreement	5/05
Celera Group	access to up to 10 cancer targets related to RNA interference-based therapeutics	exclusive two-year licensing agreement	4/08
Celera Diagnostics	new treatments for Alzheimer's disease	extended R&D agreement	9/05
ChemBridge Corp.	for Merck's drug discovery efforts	five-year discovery chemistry collaboration agreement	12/04
Codexis Inc.	Merck to be the first subscriber to Codex Biocatalyst Panels	technology collaboration	4/07
Crucell NV	Merck to have access to Crucell technology in undisclosed vaccine fields, and Crucell to have access to Merck manufacturing technology for its AdVac-based vaccines	cross-licensing agreement	12/06
CytRx	TranzFect technology in DNA-based vaccines	worldwide licensing agreement	11/00
deCode Genetics	experimental compounds	R&D agreement	2/04
Diversa Corp.	therapeutic antibodies using Diversa's MedEv platform	development agreement, expanded 6/05	1/05
DOV Pharmaceuticals	DOV 21,947 and DOV 216,303	licensing agreement, amended 8/05	8/04
Dr. Reddy's Laboratories	generic versions of Merck's Proscar and Zocor	production agreement	2/06
EiRx Therapeutics plc	EiRx to demonstrate its siRNA delivery technology	three-month research project	2/05
ExonHit Therapeutics SA	research under Patent US 6,881,571 (RNA splicing microarray)	non-exclusive licensing agreement	9/06

FoxHollow Technologies	analysis of atherosclerotic plaque from patient arteries to identify biomarkers of atherosclerotic disease progression	novel pharmacogenomics collaboration, expanded 9/06	9/05
GeneGo Inc.	use of GeneGo's MetaCore data mining suite	expanded licensing agreement	1/06
Genetronics Biomedical Corp. (now Inovio Biomedical Corp.)	MedPulser delivery system	licensing agreement	5/04
Geron Corp.	cancer vaccine that targets telomerase	development agreement	7/05
Gilead Sciences Inc.	Atripla for HIV-1 in developing countries	distribution agreement	8/06
GlycoFi	vaccines, antibodies and other proteins	strategic alliance and multiyear research agreement	12/05
HTG Inc.	ArrayPlate qNPA technology	licensing agreement	5/04
Idera Pharmaceuticals Inc.	incorporation of Idera’s Toll-like Receptor (TLR) agonists into therapeutic and prophylactic vaccines being developed by Merck for oncology, infectious diseases and Alzheimer’s disease	research, development and commercialization agreement	12/06
Ingenuity Systems	Ingenuity's Pathways Analysis	licensing agreement	12/04
Iomai Corp.	proof-of-principle preclinical studies evaluating the use of the Iomai needle-free immunostimulant patch	development agreement	4/08
International Partnership for Microbicides (IPM)	development of antiretroviral compounds to protect women from HIV	licensing agreement	10/05
KineMed Inc.	use of KineMarker to measure the modulation of the targeted metabolic pathway in Merck's Phase I clinical studies	collaboration agreement	11/06
KineMed Inc.	reverse cholesterol transport technology	licensing agreement	8/07
MediVas LLC	orally available biologics delivered using MediVas' polymer delivery system	exclusive technology evaluation and exclusive option agreements	1/07
MerLion	various therapeutic areas	R&D agreement	2/03

Metabasis Therapeutics Inc.	molecule therapeutics for the treatment of hepatitis C virus infections	R&D agreement	12/03
Metabasis Therapeutics Inc.	small molecule therapeutics to treat type II diabetes, hyperlipidemia and obesity	expanded through 12/05	6/05
Monogram Biosciences Inc.	PhenoSense and GeneSeq testing technologies for use in MK-0518	R&D and commercialization agreement	2/06
Morphosys AG	MorphoSys' HuCAL GOLD and Auto-CAL technologies	licensing agreement	12/05
Nastech Pharmaceutical Co. Inc.	Peptide YY 3-36 Nasal Spray (PYY)	five-year licensing agreement	9/04
Neurogen	novel small molecule medicines targeting the vanilloid receptor	development and commercialization agreement, Nastech reacquired rights (3/06)	na
Neuromed Pharmaceuticals Ltd.	research, development and commercialization of compounds for the treatment of pain and other neurological disorders	R&D and commercialization agreement	na
NicOx SA	antihypertensive drugs using NicOx' proprietary nitric oxide-donating technology	research collaboration and licensing agreement	na
Norak Biosciences Inc.	Norak's Transfluor technology for G protein-coupled receptor (GPCR) for use in drug discovery	development agreement	na
Ono Pharmaceutical Co. Ltd.	ONO-2506 for acute stroke	licensing agreement	na
ParAllele BioScience	genetic variations that may impact susceptibility, prognosis or response to cancer therapy	worldwide licensing agreement	na
Paratek Pharmaceuticals Inc.	PTK 0796	discovery agreement	na
PharmaDesign Inc.	PharmaDesign GPCR peptide ligand library	collaborative development and licensing agreement	na
Pierre Fabre Medicament	F50035 recombinant humanized antibody	licensing agreement	na
Rigel	investigation of ubiquitin ligases	R&D, manufacturing and	na

Pharmaceuticals Inc.	for treatments for cancer and other diseases	commercialization agreement	
Sention Inc.	Merck's mGluR5 antagonists for treating mental retardation	R&D agreement	na
Stem Cell Sciences plc	SCS' mouse neural stem cell technology	development agreement	na
Sunesis Pharmaceuticals Inc.	oral drugs for viral infections	licensing agreement	na
The J. David Gladstone Institute	drugs for neurodegenerative diseases	discovery agreement	na
Vertex Pharmaceuticals Inc.	VX-680 cancer drug	R&D collaboration agreement	na
WuXi PharmaTech Co. Ltd.	WuXi to provide a variety of chemistry-related R&D services	development agreement	na
Xenogen Corp.	Xenogen's biophotonic imaging systems and sofware	collaboration agreement, extended through 2010 and expanded (12/06)	na
Znomics Inc.	na	expanded licensing agreement	na

Source: BioScan

APPENDIX C - AstraZeneca's On-Going Cooperation Agreements (2008)

Name	Products	Content of Agreement	Date
*More than 1,700 collaborations and agreements, including the following:	drug discovery with AstraZeneca targets	research agreement	8/04
7TM Pharma A/S	combination treatment targeting LDL and HDL cholesterol and triglycerides, to begin trials of CRrestor/TriCor and Crestor/ABT-335	co-development and marketing agreement	7/06
Abbott Laboratories	research to develop fully human monoclonal antibodies to treat cancer	research alliance	10/03
Abgenix (acquired by Amgen Inc.)	Abraxis' Abraxane in the U.S.	five-and-a-half-year co-promotion agreement	4/06
Abraxis BioScience Inc.	recombinant human lactoferrin	manufacturing and research agreement	8/94
Agennix Inc.	oncology portion of Array's MEK program	R&D agreement	12/03
Array BioPharma Inc.	Fc receptor technology	research agreement, extended 11/05	10/04
Arthron Pty. Ltd.	cancer drugs	development and marketing agreement	7/05
Astex Therapeutics Ltd.	development and commercialization of AGI-1067	licensing agreement	12/05
AtheroGenics Inc.	discovery, development and commercialization of RCT enhancing compounds for the treatment of cardiovascular disease	exclusive global licensing and research collaboration agreement	7/05
Avanir Pharmaceuticals	cancer drug candidate	manufacturing agreement	7/97
Bio Science Contract Production Corp.	BioFocus to perform hit-to-lead medicinal chemistry services for AstraZeneca's respiratory	drug discovery collaboration	8/06

	and inflammatory drug discovery programs		
BioFocus DPI (service division of Galapagos NV)	biomarker discovery program in osteoarthritis	collaboration agreement	2/06
Biosystems International	Saxagliptin and Dapagliflozin	development and commercialization agreement	1/07
Bristol-Myers Squibb Co.	monoclonal antibodies for inflammatory disorders	research agreement	2004
Cambridge Antibody Technology Group plc	identification and validation of circulating biomarkers for use in conjunction with targeted cancer therapeutics	R&D collaboration	11/06
Cancer Research Technology Ltd.	discovery of novel targets for the treatment of prostate cancer	collaboration agreement	11/05
Caprion Pharmaceuticals Inc.	AstraZeneca compounds	research agreement	6/04
Cell Signaling Technology Inc.	CST to identify phosphorylation profiles and biomarkers of kinase-targeted lead compounds	collaboration agreement	4/06
Cell Signaling Technology Inc.	use of Cell Signaling's rabbit monoclonal antibody technologies to develop RmAbs to AstraZeneca oncology targets	alliance	12/06
Cell Signaling Technology Inc.	Cellectis patent family	licensing agreement	12/05
Cellectis AS	Cerep's BioPrint database	licensing agreement	5/06
Cerep SA	development of exclusive small molecule libraries to enhance AstraZeneca's global drug discovery effort	multiyear discovery collaboration	9/06
ChemBridge Corp. and ChemBridge Research Laboratories Inc.	Chirocaine (levobupivacaine) local anesthetic	worldwide licensing agreement--Chiroscience retains rights to manufacture drug, market in Japan and develop for dental office use,	3/98

		Chiroscience is responsible for U.S. and European registration process, Zeneca paid $25M licensing fee and will pay royalties on sales, Zeneca will handle marketing for drug and will invest in substantial Phase III/IV clinical and marketing program	
Chiroscience Group plc	characterization of the expression of key genes involved in colorectal cancer	collaboration agreement	9/06
CRT Ltd.	Cubicin in China and other countries in Asia, the Middle East and Africa	development and commercialization agreement	12/06
Cubist Pharmaceuticals Inc.	discovery and development of TLR-9 agonist-based therapies for the treatment of asthma and COPD	research collaboration and licensing agreement	9/06
Dynavax Technologies Corp.	Incyte's LifeSeq, LifeSeq FL and PathoSeq genomics database	database subscription	6/96
Incyte Pharmaceuticals Inc.	InforSense technology	licensing agreement	7/06
InforSense Ltd.	use of Isogenica's CIS display technology in peptide discovery	research collaboration	12/05
Isogenica Ltd.	cancer treatments	acquisition	2/08
KuDOS Pharmaceuticals Ltd.	licensing, develop and market inhibitors in combination with the hormones estrogen and progestin to treat endometriosis	licensing, developmental, and marketing agreement	1/06
Meditrina Pharmaceuticals Inc.	research on new treatments for cancer	scientific collaboration agreements	3/01
M. D. Anderson Cancer Center	drugs to treat various CNS disorders with proprietary technology	collaborative research and licensing agreement, extended 2/06	1/07

	related to metabotropic glutamate receptors (mGluRs)		
NPS Pharmaceuticals Inc.	discovery, development and commercialization of small molecule compounds that target melanocortin receptors	global licensing and research collaboration agreement	11/06
Palatin Technologies	distribution of a generic version of metoprolol succinate in the U.S.	supply and distribution agreement	1/04
Par Pharmaceutical Companies Inc.	genetics of myocardial infarction	research agreement	1/05
Perlegen Sciences Inc.	high-density whole genome association study	research agreement	8/06
Perlegen Sciences Inc.	fixed dose combinations of esomeprazole magnesium with naproxen	co-development and commercialization agreement	8/05
Pozen Inc.	CytoFab	development and commercialization agreement	2/07
Protherics plc	VelocImmune technology	licensing agreement	2004
Regeneron Pharmaceuticals Inc.	development of a novel intravenous anaesthetic agent	licensing agreement	5/05
Renovis	Selective Glucocorticoid Receptor Agonists	research collaboration and licensing agreement	9/06
Schering AG	Schering's SERD	co-development and joint commercialization agreement	7/96
Schering AG	Amphocil	worldwide marketing and distribution agreement except for the U.S., Canada, and Japan (8/93), amended	1/96
SEQUUS Pharmaceuticals Inc.	SU-5271 small molecule inhibitor for dermatological applications	exclusive worldwide licensing agreement	3/05
Silence Therapeutics plc	respiratory disease targets	license to its short-interfering RNA (siRNA) technology	7/07
SUGEN Inc.	respiratory disease area	preclinical research	12/05
Sumitomo Pharmaceuticals	TC-1734	worldwide licensing agreement	na

Targacept Inc.	novel intravenous anaesthetic agent	licensing agreement	na
Theravance	areas including addiction, cognition, anxiety, depression, stress-related disorders, and several other disease areas	preclinical and clinical research	na
University of Pennsylvania-School of Medicine	use of ViroLogic's eTag assays to test patients treated with Iressa	cancer biomarker study	na
ViroLogic	na	na	na
Xenova Group plc	na	na	na

Source: BioScan

APPENDIX D - Cooperation Among Big Pharma

The following cooperation agreements were operational in May 2008. Note that Pfizer and Roche were not included in the database and did not declare their cooperation agreements. The two firms were nevertheless included in the Table since some agreements were discovered through the specifications made by other firms.

TABLE A.3

On-Going Cooperation agreements among Big Pharma

Companies	Products	Content of Agreement	Date
Abbott Labs / AstraZeneca plc	combination treatment targeting LDL and HDL cholesterol and triglycerides, to begin trials of CRrestor/TriCor and Crestor/ABT-335	co-development and marketing agreement	7/06
Abbott Labs / Johnson & Johnson	IP for developing and commercializing RX delivery systems, drug-eluting stents and interventional products	worldwide licensing agreement	11/05
Abbott Labs / Sanofi-Aventis	trandolapril and the trandolapril/verapamil combination	acquired remaining worldwide commercial rights (except Japan)	6/04
Abbott Labs / Takeda Pharmaceutical Co. Ltd.	na	Joint Venture with the creation of *TAP Pharmaceutical Products*	
Abbott Labs / Wyeth	na	na	na
ALZA Corp. (subsidiary of J&J) / Novartis (DynaCirc CR)	Oros, oral	na	na
ALZA Corp. (subsidiary of J&J) / Bayer	Duros, transdermal	worldwide licensing agreement	1/06
ALZA Corp. (subsidiary of J&J) / GSK (Nicoderm and Clear Nicoderm CQ)	D-Trans, transdermal	na	na

ALZA Corp. (subsidiary of J&J) / Pfizer Inc. (Cardura XL Glocotrol XL)	Oros, oral	na	na
ALZA Corp. (subsidiary of J&J) / Pharmacia Corp. (Covera-HS) (now part of Pfizer)	na	na	na
Amgen / Chiron Corp. (owned by Novartis)	IL-2	licensing agreement for Chiron's U.S. and foreign patent rights	4/88
Amgen / Takeda Pharmaceutical Co. Ltd.	Takeda to take Japanese rights to 13 molecules, including Vectibix	broad, multi-target collaboration to jointly research, develop and commercialize therapeutics for the treatment of eye diseases	4/06
Amgen / AstraZeneca plc	Abraxis' Abraxane in the U.S.	R&D and licensing agreement, Axys to supply technology and Amgen to market (5/93), extended through 2/97, program taken in-house by Amgen	2/96
Amgen / F. Hoffmann-La Roche (now Roche)	G-CSF	licensing agreements	1993
Amgen / Genentech Inc. (now owned by Roche)	patents related to the manufacture and use of antibodies and related technologies	R&D and licensing agreement	8/97
Astra-Zeneca / Abbott Laboratories	research to develop fully human monoclonal antibodies to treat cancer	research alliance	10/03
Astra-Zeneca / Abgenix (acquired by Amgen Inc.)	Abraxis' Abraxane in the U.S.	five-and-a-half-year co-promotion agreement	4/06
Astra-Zeneca / Bristol-Myers Squibb Co.	monoclonal antibodies for inflammatory disorders	research agreement	2004
Astra-Zeneca / Schering AG (acquired by Bayer)	Schering's SERD	co-development and joint commercialization agreement	7/96
Astra-Zeneca / Schering AG (acquired by Bayer)	Amphocil	worldwide marketing and distribution agreement except for the U.S., Canada, and Japan (8/93), amended	1/96
Bayer Group / AstraZeneca plc	Selective Glucocorticoid Receptor Agonists	research collaboration and licensing agreement	7/05
Bayer Group / Chiron Corp. (subsidiary of Novartis)	anti-TNF MAbs to treat septic shock	licensing agreement	1989
Bayer Group / Genetics Institute (subsidiary of Wyeth)	DiscoverEase program--provides Bayer access to GI's library of novel human secreted proteins and	co-promotion agreement for the U.S.	8/97

	related database for identifying novel human therapeutics		
Bayer Group / GlaxoSmithKline plc	cerivastatin reductase inhibiting compound	exclusive licensing agreement	1997
Bayer Group / Novartis Pharma AG	PTK787/ZK 222584 (PTK/ZK)	co-promotion agreement for Europe, North America and Japan	1/05
Bayer Group / Pfizer Inc.	Schering's ADP receptor antagonist program	licensing agreement	2/05
Bayer Group / Pharmacia & Upjohn (now part of Pfizer Inc.)	animal health	research collaboration and library out-licensing	1997
Bayer Group / Takeda Chemical Industries Ltd. (Subsidiary of Takeda Pharmaceutical)	cerivastatin	na	1993
Bristol-Myers Squibb / AstraZeneca plc	Saxagliptin and Dapagliflozin	development and commercialization agreement	12/96
Bristol-Myers Squibb / Bayer HealthCare LLC (subsidiary of Bayer Group)	OTC version of Pravachol (pravastatin sodium), 20mg	sales and marketing agreement for USA	4/98
Bristol-Myers Squibb / Chiron Corp. (Subsidiary of Novartis)	Chiron's patents related to hepatitis C virus NS3 protease	non-exclusive licensing agreement	9/95
Bristol-Myers Squibb / Genetics Institute (subsidiary of Wyeth)	recombinant NPA to develop thrombolytic agent for heart attack	distribution and marketing agreement for the U.S.	5/95
Bristol-Myers Squibb / Novartis AG	BMS-234475 (peptidomimetic HIV protease inhibitor) and BMS-232632 (azapeptide inhibitor of HIV protease)	development agreement for the U.S. and Europe (1/96), extended to include Japan	na
Bristol-Myers Squibb / Sanofi Winthrop Pharmaceuticals (subsidiary of Sanofi-Aventis)	SR 47436 small molecule antagonist to the angiotensin II receptor and clopidogrel	worldwide rights	na
Centocor Inc. (subsidiary of J&J) / Roche Healthcare Ltd. (subsidiary of Roche)	Retevase (reteplase recombinant plasminogen activator) for acute myocardial infarction	as part of its purchase of Corange, (the parent company of Boehringer Mannheim GmbH, the manufacturer and marketer of Retevase), the FTC required Roche to divest Retevase	3/98
Centocor Inc. (subsidiary of J&J) / Schering-Plough	remicade and golimumab	licensing agreement	12/07

Corp.			
Centocor Inc. (subsidiary of J&J) / Glaxo Wellcome plc (now GlaxoSmith Kline plc)	Panorex and other MAb-based oncology products	marketing agreement	1/95
Chiron Corp. (owned by Novartis) / Aventis Pasteur MSD (subsidiary of Sanofi-Aventis)	Menjugate and Fluad	co-marketing agreement (Europe)	8/00
Chiron Corp. (owned by Novartis) / F. Hoffman La-Roche (now Roche)	development and sale of small-molecule drugs against hepatitis C targets	nonexclusive licensing agreement	8/00
Chiron Corp. (owned by Novartis) / F. Hoffmann-La Roche (now Roche)	probe-based clinical diagnostics for hepatitis C virus	patent license agreement	7/95
Chiron Corp. (owned by Novartis) / F. Hoffmann-La Roche (now Roche)	Vitrasert intraocular implant	marketing and joint promotion agreement	1996
Chiron Corp. (owned by Novartis) / G.D. Searle & Co. (now part of Pfizer)	Tifacogin (Tissue Factor Pathway Inhibitor (TFPI))	cross-licensing agreement--Searle and Chiron will collaborate as equal partners in all R&D. Chiron will manufacture and Searle will market, although both will promote product worldwide	3/95
Chiron Corp. (owned by Novartis) / Genetics Institute (subsidiary of Wyeth)	Genetics Institute's protein library	partnership agreement	7/98
Chiron Corp. (owned by Novartis) / Pharmacia & Upjohn (now part of Pfizer Inc.)	small-molecule inhibitors of hepatitis C virus	development agreement--P&U to pay Chiron up-front payment, but companies will contribute equally to R&D costs and will share worldwide marketing rights, Chriron will provide its HCV knowledge plus non-exclusive rights to both patented and patent-pending HCV targets	na
Chiron Corp. (owned by Novartis) / Rhone-Poulenc Rorer Inc. (now Sanofi-Aventis)	HSV-tk (Herpes simplex-thymidine kinase) gene for gene therapy	licensing agreement	na
Chugai Pharmaceutical Co. Ltd. (majority ownership by Roche) / Genetics Institute (subsidiary of Wyeth)	Epogin rhEPO	manufacturing and marketing agreement for Japan	10/97
Chugai Pharmaceutical	Genetics Institute's	partnership agreement	1/97

Co. Ltd. (majority ownership by Roche) / Genetics Institute (subsidiary of Wyeth)	DiscoverEase protein library		
Chugai Pharmaceutical Co. Ltd. (majority ownership by Roche) / Rhone-Poulenc Rorer (now Sanofi-Aventis)	Amoban	Chugai to market in Japan	6/90
Chugai Pharmaceutical Co. Ltd. (majority ownership by Roche) / Rhone-Poulenc Rorer (now Sanofi-Aventis)	Granocyte (rhG-CSF)	joint venture to develop and market in Europe	7/97
Chugai Pharmaceutical Co. Ltd. (majority ownership by Roche) / Rhone-Poulenc Rorer (now Sanofi-Aventis)	Taxotere (docetaxel)	licensing agreement in Japan	6/94
Eli Lilly / Centocor Inc. (subsidiary of J&J)	Centocor's ReoPro	$125M marketing collaboration (7/92), amended--Lilly no longer has exclusive right to buy ReoPro for resale in Japan	7/96
Eli Lilly / Chugai Pharmaceutical Co. Ltd. (majority ownership by Roche)	raloxifene for osteoporosis	joint development and marketing agreement for Japan	12/95
Eli Lilly / Genentech Inc. (majority ownership by Roche)	Humulin (rhinsulin)	licensing agreement	8/93
Genentech (owned by Roche) / Pharmacia & Upjohn (now part of Pfizer)	thrombopoietin (TPO)	worldwide licensing and codevelopment agreement--P&U made $12M payment at signing and will pay additional $23M in licensing over three years, P&U will pay final transfer payment and royalties if product is successfully commercialized, Genentech will conduct trials in myeloablative therapy and P&U will handle testing for all other indications	na
GlaxoSmithKline / Roche Palo Alto (Subsidiary of Roche)	Boniva	co-development and co-marketing agreement in all countries except Japan	12/01
Johnson & Johnson / Abbott Laboratories	consumer diagnostics and automated immunochematology testing	joint development agreement	9/89

Johnson & Johnson / Abbott Laboratories	IP for developing and commercializing RX delivery systems, drug-eluting stents and interventional products	worldwide licensing agreement	11/05
Johnson & Johnson / Abbott Laboratories / Chiron Corp. (owned by Novartis)	hepatitis C diagnostic products for blood banks, hospitals and laboratories	collaborative development and supply agreement	9/89
Johnson & Johnson / Amgen Inc.	EPO	research agreement through Ortho Pharmaceuticals--J&J has U.S. marketing rights under the brand name Eprex for treating most forms of anemia resulting from surgery-related infections and other ailments	1988
Johnson & Johnson / Merck & Co.	OTC medicines	50/50 joint venture called Johnson & Johnson Merck Consumer Pharmaceuticals Co.	na
Merck / Astra AB (now part of Astra-Zeneca)	na	joint venture called *Astra Merck*	11/94
Merck / Chugai Pharmaceutical (majority ownership by Roche)	na	joint-venture called *Chugai MSD*	na
Merck / Rhone-Poulenc (now part of Sanofi-Aventis)	na	joint-venture called *Merial Animal Health*	na
Merck / Sanofi-Pasteur (subsidiary of Sanofi-Aventis)	na	joint-venture called *Sanofi Pasteur MSD*	na
Novartis / ALZA Corp. (subsidiary of J&J)	transdermal drug delivery systems for estradiol, scopolamine and nitroglycerine	marketing agreement	2002
Novartis / Rhone-Poulenc Rorer Inc. (now Sanofi-Aventis)	development and commercialization of SeBo's oral phosphate binder to treat elevated phosphate levels	worldwide marketing agreement	7/98
Novartis / Schering-Plough Corp.	Senju's Y39983--glaucoma treatment	global collaboration	8/06
Sanofi-Aventis / Bristol-Myers Squibb Co.	clopidogrel and angiotensin II receptor antagonist	joint development and marketing agreement	6/93
Sanofi-Aventis / Roche	shikimic acid by fermentation for Roche's	production agreement	1996

	Tamiflu supply chain		
Schering-Plough / Bayer Corp.	Bayer's primary care pharmaceutical products	marketing and distribution agreement (USA)	9/04
Schering-Plough / Centocor Inc. (subsidiary of J&J)	Avakine (infliximab) MAb for Crohn's disease and rheumatoid arthritis	$50M marketing agreement--Centocor gets $20M up front and $30M in milestones, excludes the U.S., Japan and portions of the Far East, companies will divide profits and will share certain internal and external development expenses	4/98
Schering-Plough / Centocor Inc. (subsidiary of J&J)	CNTO 148	licensing agreement	8/05
Schering-Plough / GlaxoSmithKline plc	gene sequence database	$55M 'co-opetition' agreement--Schering-Plough, HGS and SmithKline Beecham plc will cooperate and compete in development of small-molecule drugs	7/96
Schering-Plough / Merck & Co.	cholesterol management and respiratory therapeutics	R&D and marketing	7/05
Schering-Plough / Novartis AG	development and commercialization of a once-daily inhaled fixed-dose combination therapy for the treatment of asthma and COPD	global collaboration	11/05
Schering-Plough / Wyeth	interleukin-11 (IL-11)	Schering-Plough to transfer all rights to AHPC for undisclosed cash amount	na
Takeda / Abbott Laboratories	drug for prostate cancer and ulcer	joint venture called TAP Holdings to market drug developed by Takeda	8/77
Takeda / McNeil Consumer Products Co. (subsidiary of J&J)	McNeil's OTC products	marketing agreement for Japan	1997
Takeda / Pharmacia & Upjohn (now part of Pfizer)	smoking cessation	joint marketing agreement--Takeda to sell P&U smoking cessation products in Japan	1996
Wyeth / Genentech Inc. (majority ownership by Roche)	Herceptin (trastuzumab)	manufacturing agreement	9/06
Wyeth / Immunex (subsidiary of Amgen)	Enbrel	marketing agreement	na

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