

***Political regimes, technological regimes and innovation in the evolution of the pharmaceutical industry in the USA and in Europe.***

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FIRST PRELIMINARY AND VERY ROUGH DRAFT

***Abstract***

This paper examines the evolving interplay between “policy regimes” and “technological regimes” in the pharmaceutical industry and how this interaction contributed in the long run to shape the innovative performance in the USA and in various European countries. We discuss the various and shifting motivations underlying regulatory interventions as well as the different solutions that have been given to these issues over time and across countries. The paper argues that policies and institutional design affected industry evolution, sometimes consciously, sometimes through the unintended effects of interventions taken for reasons largely independent of considerations related to the performance of the industry. These interventions and the evolving institutional structures influenced the patterns of accumulation of competencies, the selection mechanisms and the incentive structures to engage in innovative activities in many different, and sometimes indirect, ways. Policies themselves are largely adaptive and are embedded in and are shaped by specific institutional and political environments and by accumulated competencies.

Given the inherent trade-offs and tensions between alternative goals and the variety of motivations and instruments underlying regulation, it is argued that the relations between policy regimes and industrial change are better understood as a process of dynamic disequilibrium. In the last section of the paper, however, some tentative generalizations are suggested about the relationships between forms and intensity of competition, patterns of organization of the processes of competence accumulation, and innovative performance.

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## ***1. Introduction***

The history of the world pharmaceutical industry has been marked by a series of technological and institutional changes that have led to deep transformations in firms' organization, in market structure and in the patterns of competition, and in competitiveness.

On the one hand, scientific progress and subsequent waves of technological innovations have continuously transformed the prospects and the processes of drug discovery and development. On the other hand, different sets of motives led to regulatory interventions. Ever since its inception, pharmaceuticals have been heavily regulated, for a variety of different reasons and objectives and through a wide spectrum of instruments, the importance of which has been changing over time and across countries.

Considerations linked to consumer protection have led to increasingly stringent requirements for the approval of new drugs and they have implied larger and more costly clinical trials. The presence of significant information asymmetries in the market for drugs coupled with fundamental considerations of social and economic equity have been often used to justify the introduction of various forms of price regulation. The emergence of the welfare state first and the subsequent rise of healthcare and prescription drug spending later have induced first a rapid expansion of demand and then a series of cost containment policies. Developments in legislation and in courts' interpretation of issues concerning intellectual property rights have also had significant impacts on patterns of competition and industrial evolution. Last, but certainly not least, the institutional setups governing the systems of fundamental scientific research have profoundly affected the ability to discover, develop and commercialize new drugs.

This paper examines the evolving interplay between "policy regimes" and "technological regimes" in this industry and how this interaction contributed in the long run to shape the structure and the innovative performance of pharmaceuticals in the USA and in various European countries. We discuss the various and shifting motivations underlying regulatory interventions as well as the different solutions that have been given to these issues over time and across countries.

However, in order to restrict somewhat such a wide and complex sets of issues, we focus mainly on the relationships between regulation and innovation<sup>1</sup>. The paper argues that indeed policies and institutional design deeply affected innovation and industry evolution, sometimes consciously, sometimes through the unintended effects of interventions taken for reasons by and large independent of considerations related to the performance of the industry. These interventions and the evolving institutional structures influenced the patterns of accumulation of competencies, the selection mechanisms and the incentive structures to engage in innovative activities in many different, and sometimes indirect, ways. Policies themselves are largely adaptive and are embedded in and are shaped by specific institutional and political environments and by accumulated competencies.

Given the inherent trade-offs and tensions between alternative goals and the variety of motivations and instruments underlying regulation, we argue that no simple relation can be identified between specific forms of intervention and innovative performance. Rather, the relations between policy regimes and industrial change are better understood as a process of dynamic disequilibrium and co-evolution within a changing network of relations and activities which comprises different agents, interests and competencies.

The paper is organized as follows. Section 2 briefly summarizes the main (economic) arguments that might suggest various forms of regulation in pharmaceuticals. Then the paper goes on presenting the evolution of regulation over time in the USA and in the main European countries. We develop our discussion broadly and roughly dividing the history of the industry into three main epochs: the emergence and early development (until War World II) (Section 3), the “Golden age and the Welfare State era” (from War World II until approximately the mid-Seventies) (Section 4), the “Age of Molecular Biology and Cost-containment” (Section 5). In each period, we focus on the main regulatory interventions and institutional set-ups that have impacted on the innovative performance of the industry. In particular, we look at the

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<sup>1</sup> This emphasis on innovation is partly justified by the obvious relevance that technological change has in this industry. More generally, we are convinced that pharmaceuticals are almost a textbook case where the intricacies of dynamic vs. static competition are more clearly expressed. In this respect, all throughout the paper, we are ready to accept the working (and certainly not entirely justified) hypothesis that broadly speaking more innovation is better than less innovation, both in terms of pure economic efficiency but also (and much less unambiguously) in terms of welfare and perhaps even social justice.

procedures for product approvals, patent regimes, price controls and measures aiming at influencing the demand for drugs and finally also at the structure and functioning of the public research systems.

In the last section, some tentative generalizations are suggested about the relationships between forms and intensity of competition, patterns of organization of the processes of competence accumulation, and innovative performance.

## ***2. The Political Economy of the Pharmaceutical Industry: Back to the Basics***

The pharmaceutical industry produces products – drugs – which are directed to satisfy consumer needs in an area – health care – whose importance for the society is fundamental and rapidly increasing. Health care and therapeutics are among the most relevant issues in the definition of the concepts of welfare, justice and democracy in the new century. Moreover, pharmaceuticals are – and have always been - a large, high-growth, globalized, science-based and innovation intensive industry. The patterns of competition in this industry are – perhaps an extreme – example of what economists sometimes call “dynamic competition”. This industry has shown so far a remarkable track-record in innovativeness, economic and financial performance and (although not completely uncontroversially) welfare. On the other hand, it has sometimes generated disasters (e.g. thalidomide) and it cannot avoid being involved in tragedies like e.g. the inability to grant access to drugs for curing HIV in Africa.

Under both perspectives – the demand side and the supply side – this industry is characterized by features that make the standard static competitive normative model inadequate. In this industry, perfect competition does not necessarily maximize social welfare. Nor it should be taken for granted that competition is necessarily better than other forms of organization of the production and distribution of drugs.

Thus, it is no surprise that this industry is and has always been heavily regulated. There is a huge literature about the reasons explaining public intervention in the pharmaceutical market. To begin with, the nature of the products involved is quite peculiar, and makes the analysis of the market to large extent a social rather than a purely economic issue. Regardless of the different attitudes (across time and countries) towards the industry and its regulation, the main goal of state intervention has always

been to guarantee the access to safe (and later on) efficacious drugs to the largest possible share of the population. Thus, a primary reason for regulation is based on equity considerations. Everybody should have access to drugs, especially (new) expensive ones.

A related – but different, because it is argued in terms of economic efficiency - argument refers to some peculiar features of the market for drugs. Let us recall some of them:

- a) The market for drugs is inherently characterized by information asymmetry. Producers have “more information” on the quality of the drug than consumers do. The consumer is normally ill informed about many characteristics of drugs. It is the prescribing doctor who makes the decision, but even doctors often do not know in detail the properties of a drug, especially when a drug is new.
- b) Moreover, it is observed that much of the information available to physicians is provided by the companies themselves. As a consequence, an external assessment of the safety of the drug (and starting from the early Sixties of its efficacy) may be necessary to prevent damage to the consumers. A slightly different way to express this argument is that drugs are merit goods.
- c) Given the value that users may attribute to the product, especially in extreme cases, demand elasticity tends to be low. Moreover, most consumers are insured (privately or publicly) against at least a part of the cost of prescription drugs, so they are only partially interested in drug prices. The prescribing physicians alike are not completely sensitive to prices, both because they will not pay for the prescribed drugs, and because the respect of professional norms makes them more attentive to the safety and therapeutic value of medicines. Despite their role of scientific experts, however, physicians’ prescribing behavior does not seem immune to other forces, as advertising and brand loyalty, and seem to follow routinary patterns (Jacobzone, 2000). Some more recent evidence would seem to suggest that both patients and doctors are much more price and quality conscious than it was usually assumed. Yet, to date, economic analysis has not fully accounted for these practices, and evidence about their impacts on decision is rather anecdotal. In any case, the case has been made that producers could try to exploit this asymmetry and the low demand

elasticity by charging higher prices, especially if some form of market power is present on the supply side.

- d) A further set of reasons for regulation refers to cost containment. In countries where a national health service exists or when in any case there is a third payer (typically, an insurer), demand elasticity to price tends to be lower than it would otherwise have been the case. This may lead to price increases by firms enjoying market power. Moreover, as a consequence, the absence of any countervailing measure is likely to lead to an explosion of public expenditures, because neither the patients nor the physicians ultimately pay for the drug. Thus, the governments may act as monopsonist and through various instruments tend to reduce drug prices.
- e) In fact the industry presents some peculiar aspects also on the supply side and elements of market power and non-price competition are certainly crucial. First, pharmaceutical industry is a science-based sector, where scientific knowledge plays a central role and is only in part appropriable. Technological innovation plays a crucial role in competition. Part of the knowledge which is used to produce new, better drugs is generated by and/or based on publicly funded scientific research, in principle available to everybody through publication. Thus, pharmaceutical companies are partly “subsidized” through publicly funded research. Part of the relevant knowledge is instead private. Producers are attributed (temporary) monopoly power through patent protection. Absent such protection, profit-seeking firms would not invest in research or would under-invest as compared to social optimum. Indeed, pharmaceuticals are one of the few industries where patents are considered very important mechanisms of appropriability of the economic outcomes of innovation. Given the existence of (even temporary) monopoly power, regulation might therefore be justified as a mechanism to countervail monopolistic pricing. This would be particularly the case if and to the extent that innovation exhibits some forms of cumulativeness, like e.g. success-breeds-success phenomena through the reinvestment of profits in R&D, or static and dynamic economies of scale and scope in research, existence of other mechanisms for appropriating rents stemming from innovation and other mechanisms that allow for the creation of long lasting competitive advantages.

f) Advertising is one prominent and relevant example in this case. Not only advertising might be misleading. In any case, it tends to generate brand loyalty effects and therefore some form of dynamic increasing returns. Both R&D expenditures and advertising involve high fixed, sunk costs, that are a powerful mechanisms creating concentration. Thus, the supply side is inevitably characterized by monopoly power, which might lead to excessive prices. But, even more important, the prevalent mode of competition is not the standard static model, but dynamic competition where some of the conventional efficiency properties of competition may not apply. In part, this attitude was reflected in the frequent accusations of excessive profits enjoyed by the industry and of aggressive and misleading marketing practices by the pharmaceutical companies. These issues, for example, figured prominently in the debates within the Kefauver Committee (see Comanor 1986 for a survey). On the other hand, it is precisely the dynamic connotation of competition in this industry and the weight of fixed, sunk costs that might justify the existence of some degree of monopolistic power. However, it is observed that concentration in the industry is quite low, both at the aggregate level, and also in specific therapeutic categories and that market shares gained through the introduction of new products are rapidly eroded even before patent expiry by imitation, inventing around, etc... Thus, the debate here is on the actual degree and patterns of competition.

The policy-maker thus faces very different and contrasting objectives. In brief, the goal of efficacy and safety of drugs, and equity in their availability to populations, goes along with the needs for firms of adequate economic incentives (profits) to induce investment in research on new medicines. In recent years, the rise of the issue of the containment of drug expenditures has added a further dimension to the problem, even in those countries, like the US, where the health care system is almost completely private, because the government has still a large stake in terms of financial commitment.

Moreover, the industry has experienced, along a century of history, at some major technological and scientific breakthroughs, as the “antibiotic revolution” in the 30’s and the emergence of biotechnology. Such events have substantially changed the industry dynamics. The possibility to discover and develop new drugs was (and is) not just an occasion for firms to make profit. It also has changed the procedures, forms of organization and costs of research as well as the attitudes of people towards health care.

The definition of health care itself, and then people needs, depends on the status of scientific and technological progress. Likewise, demand pressure may stimulate research of new products.

Not surprisingly then, the solutions to these problems and trade-offs has been changing over time and across countries. During the last 70 years, countries have provided different and even contrasting policy approaches to such issues. A systematic examination of the motivations of such variegated and changing policy orientations would go far beyond the scope of this paper (and of the authors' competencies). Much less ambitiously, our discussion suggests that the following broad factors have had an important role:

i) The different perceptions about drugs and more generally health care: to what extent are they conceived as a public good, or as an externality or – even more broadly - a “human right”?

ii) The state of knowledge about diseases and their possible cures as well as the distribution of such knowledge among patients, doctors, companies, scientists, regulatory institutions. More generally, technological change influences on the one hand the prospects, the directions of - and, jointly with the nature of the appropriability regimes - the economic incentives to innovative activities; on the other hand, it contributes to define what is considered as safe and efficacious and more generically, the extent to which access to various classes of drugs is a public good, an externality or a basic right of any citizen or human being. The distribution of knowledge defines the levels and forms of information asymmetries, the degree to which patients can exert consumer sovereignty, the languages that are used in the processes of negotiation and bargaining between public agencies, firms, the medical community and patients, etc...

iii) The broad – often pre-analytically determined - perceptions about the role that the State should play in the economy and in other spheres of human life; but also - and perhaps more important - the administrative structures, the rules and the routines that define the processes of policy making.

iv) Quite obviously, power relations between the relevant agents.

Put it differently, it is almost a truism that policies are shaped by a large variety of macro and micro factors. What is perhaps a bit less obvious is that policies are defined within a dense network of variegated interactions between the dynamics of

knowledge, of institutions, of values of different agents, each characterized by differentiated motivations, trajectories and behavior. Thus, with specific reference to the case of innovation in pharmaceuticals - it may be somewhat misleading to frame this kind of issues simply in terms of “market failures”. Rather, it might be sometimes more useful to reason in terms of “system failures”, explicitly recognizing that innovation originates in specific sectoral, national/ regional/international systems, which comprise varied interactions: from almost pure market transactions, to competition and cooperation, to all sorts of the so-called intermediate and hybrid forms of organization, to command-and control interventions, etc. (McKelvey and Orsenigo, 2001).

Thus, policies and forms of regulation cannot be only or simply evaluated in terms of their ability to remediate to some supposed market failures. They respond also to other perceived needs and criteria and have an inner logic which does not necessarily coincide with purely efficiency based arguments. On the other hand, the virtues and failures of markets and competition cannot be simply assessed in an excessively abstract way, but with reference to other well specified alternatives.

In what follows, we shall examine the main traits of the evolution of regulation across the major countries over time. The patterns of development of the pharmaceutical industry have been extensively analyzed by several scholars. Rather than telling the same story once again, we pick up some particularly important and relevant themes for our argument. This paper relies especially on the work by Chandler 1990 and 1998, Galambos and Sewell 1996, Galambos and Sturchio 1996, Gambardella 1995, Lamoreaux and Galambos 1997, Orsenigo 1989, Schwartzman 1976 and Henderson, Orsenigo and Pisano, 1999.

In very general terms, the history of the pharmaceutical industry is usually and usefully (although perhaps imperfectly) divided into three major epochs. The first epoch is roughly the period 1850-1945. The second epoch is roughly the period 1945 to the early 1980s. The third epoch is from the early 1980s through the present time.

### ***3. The early stages of the pharmaceutical industry***

The first epoch corresponds roughly to the period 1850-1945. This is the period in which drugs were closely related to chemicals, especially with the emergence of the

synthetic dye industry in Germany and Switzerland. In this epoch little new drug development occurred and the minimal research that was conducted was based on relatively primitive methods. Initially, Swiss and German chemical companies such as Ciba, Sandoz, Bayer, and Hoechst leveraged their technical competencies in organic chemistry and dyestuffs in order to begin to manufacture drugs (usually based on synthetic dyes) later in 19th century. Up until World War I German companies dominated the industry, producing approximately 80% of the world's pharmaceutical output, although firms in other geographic localities, mainly the USA and the UK, were also moving into pharmaceuticals.

In those years, regulation was not strongly developed. However, as the industry started to evolve, regulation began to take shape, also under the influence of the industry itself.

The primary form of intervention concerned safety. In the USA, the Pure Food & Drug Act (1906) prohibited the adulteration and mislabeling of food and drugs sold in the interstate commerce. Other forms of safety regulation were present in most European countries, but they were largely ineffective and unsystematic. This should not be particularly surprising. The notion of safety itself is largely defined by the current state of knowledge about diseases and the mechanisms of action of drugs. In those early years, the pharmaceutical industry was not tightly linked to formal science nor it was characterized by extensive in-house research and development (R&D) for new drugs. Until the 1930s, when sulfonamide was discovered, drug companies undertook little formal research and little formal testing was done to ensure either safety, let alone efficacy. Thus, the history of safety control has been one of continuous (and highly uncertain) "running after" the evolution of the industry scientific bases. This has often taken the form of answers to scandals and tragedies and has been inevitably, a highly uncertain process, especially in the periods of shifting technological paradigms.

In 1937 the elixir of sulfanilamide, containing the poisonous solvent diethylene glycol, killed 107 persons, many of them children, dramatizing the need to establish drug safety before marketing and showing the inadequacy of previous legislation. In the USA, the Food, Drugs and Cosmetic Act was passed in 1938 with the aim to fill this gap. The Act introduced a requirement for New Drug Application (NDA) and attributed

to a public authority, the Food and Drug Administration, the power to decide about the safety of each drug.

Another part of the act increased the amount of information that a drug label was required to contain. The regulations applying this provision created for the first time a distinction between over-the-counter drugs that had detailed labels and prescription drugs, which had limited labels but could not be sold without a doctor's prescription. Up to then, any non-narcotic drug could be sold either way. The attempt to solve one of the peculiar problems of the pharmaceutical market, i.e. the information asymmetries between consumers and producer (furthermore, in a changing and uncertain technological environment) created another peculiarity of the sector: the "interposition" of prescribing, non-paying physicians in purchasing decisions, for a growing number of drugs. Together with the emergence of health insurance schemes (private in the US, and public in most European countries and Japan, as we shall see), this contributed to the low price elasticity of drug demand, which in turn, is one of the reason explaining price controls to insure the availability of medicines for the largest share of population and, later, as a form of cost-containment.

The other important form of regulation concerned instead patents. Both the USA and the UK had a legislation that allowed product patents, whereas Germany had no unified patent law until 1877. The Patent Law of 1877 instituted a rigorous examination by the Patent Office before a patent would be granted. This examination was meant to determine whether the application did actually implied a novel product or process and therefore to define precisely the scope of the claim. The rigor of the examination process – much tougher as compared to the USA and especially the UK, at least until 1905 - made a patent legally much more secure once it was granted, by reducing the risk of litigation. In turn, this facilitated the creation of a market for patents, whereas in the UK patents were often the subject of intensive, uncertain and costly litigation. The German law, however, allowed only process patents and required that they were worked within the country, whereas this was not the case in the USA and – in practice - in the UK<sup>2</sup>. As Peter Murmann (2001) argues persuasively, these features of the patent system

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<sup>2</sup> Other important aspects of the German Law and of the reform act of 1891 are discussed in Murmann (2001). They concerned essentially the reversion of the burden of proof on the accused party in infringement suits and the possibility of filing extensions to the original patent. These provisions significantly raised the degree of protection afforded by a patent. Moreover, the introduction of the (PTO)

were very important in establishing the German dominance in chemicals and in pharmaceuticals. The concession of strong product patents early on in the history of the British and French industry prevented the entry of new firms and gave to few companies monopoly profits without having to develop strong competitive capabilities. Moreover, frequent and costly litigation over patents among British firms further weakened them. Conversely, the German system allowed the industry – not simply individual monopolists – to grow and to construct such competencies, also exploiting the ample possibilities of infringing British patents. As the German industry established itself as the world leader in chemicals, the domestic patent regime began to act as a reinforcing mechanism, providing further incentives to innovate – especially as it concerned processes – and to build systematic R&D efforts. Moreover, German companies were protected by foreign competition, whereas they were able at the same time to take advantage on the one hand of the loose enforcement system prevailing in Britain and of the possibility to resort to the US patent system for obtaining the product patents necessary for the processes of internationalization, on the other. The absence of product patent protection at home – to the extent that it promoted diffusion and trade of knowledge - was one element contributing to the formation of a formal and informal market for technology and to the collusive character of the German chemical industry. On the other hand, the existence of a strong technical and scientific base and the development of technical societies made it possible for the patent regime to work in the interests of the industry. Indeed, the German industry was very active in eliciting changes in legislation and in actually creating an appropriability regime favorable to the industry itself. Conversely, in the British case the weaker technical and scientific background on the one hand and the relative fragility of the domestic industry on the other made it more difficult to design and impose a robust patent regime.

In sum, patent legislation evolved and worked differently across countries also as a function of the scientific and technological capabilities characterizing each national industry. Incentives to innovate were shaped by patent laws but the appropriability

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possibility of oral arguments before the patent office constituted – according to Peter Murmann - an important opportunity for the development of an arena where industrialists could meet and talk about issues of mutual interest, thereby strengthening the identity of the German industry as whole and its political power (and perhaps the degree of collusion).

regime itself was deeply influenced and modified by the competencies and capabilities of the industry.

#### *4. The emergence and development of regulation in the golden age of pharmaceuticals*

The period that runs approximately from 1945 to the mid Seventies is often called the golden age of pharmaceuticals. During the war, the U.S. and British governments organized a massive research and production effort that focused on commercial production techniques and chemical structure analysis. More than 20 companies, several universities, and the Department of Agriculture took part in the Anglo-Saxon effort. The commercialization of penicillin marked a watershed in the industry's development. Due partially to the technical experience and organizational capabilities accumulated through the intense wartime effort to develop penicillin, as well as to the recognition that drug development could be highly profitable, pharmaceutical companies embarked on a period of massive investment in R&D. Companies built large-scale internal R&D capabilities.

At the same time there was a very significant shift in the institutional structure surrounding the industry. First, whereas before the war, public support for health related research had been quite modest, it boomed to unprecedented levels after the war. Thus, science push and science connections began in earnest. Second, the development of the Welfare State - especially of National Healthcare systems - provided a rich, "organized" and regulated market for drugs, even if obviously the features varied drastically across countries.

In this period, the German and Swiss industries remained top innovators and continued to dominate the industry. Indeed, it is worth remembering that, despite the requisition of German patents at the end of the war, the big German giants which emerged after the split-up of IG Farben, regained their leadership very quickly. In these and other countries, smaller and less innovative firms prospered in their domestic markets, through processes of imitation, inventing-around and the production and marketing of drugs under license or after patent expiration. However, in the post-war

years the American industry joined the core of the worldwide industry leaders and started quickly to set the stage for its subsequent dominance.

#### *4.1 Demand Growth, the Development of Health Care Systems and Price Regulation*

The first fundamental change in this second epoch was related to the development of health care systems. In general, the rise and consolidation of the Welfare State implied a strong increase in the demand for drugs. Interestingly enough, these developments took very different forms across countries, and thereby had differentiated effects on the profits of those firms with a significant share in domestic markets.

The USA was the only country where a national health service was not created. Yet, other factors – primarily the size of the domestic market and the high prices of drugs - supported a fast growth in demand. The fragmented structure of health care markets and the consequent low bargaining power of buyers further protected pharmaceutical companies' rents from product innovation. Unlike most European countries (with the exception of Germany and the Netherlands) and Japan, drug prices in the U.S. were unregulated by government intervention. Until the mid-1980s the overwhelming majority of drugs were marketed directly to physicians who largely made the key purchasing decisions by deciding which drug to prescribe. The ultimate customers - patients - had little bargaining power, even in those instances where multiple drugs were available for the same condition. Because insurance companies generally did not cover prescription drugs (in 1960, only 4% of prescription drug expenditures were funded by third-party payers), neither did insurance companies provide a major source of pricing leverage. Pharmaceutical companies were afforded a relatively high degree of pricing flexibility. This pricing flexibility, in turn, contributed to the high return, and hence also firm profitability of investments in drug R&D for future block-busters.

In most European countries and in Japan, prices of drugs were subject to various forms of direct or indirect control, for different reasons.

The argument in favor of price regulation was a mixture between an aspiration to equity and considerations about the imperfections of the drug market, especially as information asymmetries were concerned (although this was not the terminology that

was used). Mainly, price regulation was considered as necessary mechanism for countervailing monopolistic pricing and “excessive profits” earned by the industry. In part, this attitude was reflected in the frequent accusations of excessive profits enjoyed by the industry and of aggressive and misleading marketing practices by the pharmaceutical companies. These issues figured prominently also in the USA, and were brought to the public debate in the Kefauver Committee.

Criticisms about the high prices arose first in late 50s and 60s: the Kefauver Committee denounced the disproportionate profit margins that US drug firms were earning, thanks to high prices and much lower costs than what was publicized. Consumer protection, even in terms of affordable access to medicines, seemed to be the main concern. The Kefauver Committee set on an intense debate, supported by a large variety of rigorous studies (see Comanor 1986 for a survey)<sup>3</sup>. However, the results were largely inconclusive and the main outcome of the Committee was the introduction of tougher procedures for product approval, without any direct intervention on the pricing of drugs. Policies on price (and, more generally, expenditure) regulation were much more controversial. Recall the trade-offs that governments face in regulating the industry. In the case of product approval, safety arguments tend to be dominant with respect to others (even though the debate, as stated above, has been quite intense in some periods). Moreover, it seemed easier to reach consensus on scientific arguments, as well as on the economic terms of the question, such as the problem of information asymmetries, as far as safety and efficacy were concerned rather than on price regulation. In such field, the different objectives at stake (avoid patients deterrence for financial reasons, enhancing drug research and discovery, controlling public expenditure) are taken as almost equally important. The adopted solutions, further, depend on a number of heterogeneous factors, such as the characteristics of the national health insurance systems (if there is one), and the historical patterns of relations between governments and the industry.

In the postwar years, cost consideration certainly played an important role ever since the creation of the National Health Systems, especially in the UK. Government

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<sup>3</sup> It is certainly interesting and instructive to re-read the huge – mainly empirical – economic literature spurred by the discussion. Although such research did not indicate in the end any clear-cut result, the spirit and the quality of the debate looks certainly impressive, in terms of the relevance to the specific (difficult) issues that were analyzed and of the rigor of the analyses.

intervention on prices was seen essentially as an attempt to exert monopsonistic power against the industry. However, the belief was diffused that the general health conditions would improve over time (mainly as consequence of rising standards of living) and it seems that other objectives, rather than cost containment *per se* were considered as comparatively more important until the 1980s.

Finally, price regulation has often been used (in most cases implicitly) as an industrial policy tool, to protect and/or to promote national industries.

Both the objectives and the instruments of price controls differed widely across European countries and Japan, according to the role taken by the State as customer of drugs and partly because of entrenched different attitudes and expectations about the role of the Welfare State as well as of deeply ingrained “policy styles” or “routines”.

In the UK, the Voluntary Price Regulation Scheme (later relabeled the Pharmaceutical Price Regulation Scheme) was established in 1957, and defined a cap to the overall rate of return of firms, regardless the pricing policy on each single product. The profit margin was negotiated by each firm with the Department of Health and it was designed to assure each of them an appropriate return on capital investment including research conducted in the UK and was set higher for export oriented firms. In general, this scheme tended to act as a non-tariff barrier which favored both British and foreign R&D intensive companies which operated directly in the UK. Conversely, it tended to penalize weak, imitative firms as well as those foreign competitors (primarily the Germans) trying to enter the British market without direct innovative effort *in loco* (Burstall, 1985, Thomas, 1994). The term “voluntary” expresses quite well the nature of the system: it was not established by law, but firms participated on a voluntary basis, and profit caps were determined and revised through periodical bargaining between the Association of British Pharmaceutical Industry and the Department of Health and Social Services<sup>4</sup>. Many scholars have highlighted the peculiarity of this flexible and informal system, based on permanent forums and mutual recognition and trust, and quite stable over time. However, it has been also noted that firms have long enjoyed a relevant bargaining power, due to informative advantages. This led to the definition of a profit

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<sup>4</sup> A similar system has been adopted in the regulation of public utilities under private ownership such as electricity and water supply.

rate cap well above the world average, and, on the other side, provided low incentives to reduce costs.

Germany (but also other countries like the Netherlands) represents instead an interesting case in which the presence of universal health insurance, provided by private sickness fund (the system dates back to Bismarck era) has not been accompanied by some form of price control. Several explanations, regarding economic as well as more “systemic” factors, have been provided. First of all, as the participation to the fund is compulsory and is financed in large part by employers, there has not been concern about the provision of drugs and other health services for almost all the population. Moreover, thanks to the sustained rates of economic growth the issue of cost containment was not a major one in the political agenda. Thus, drug prices were quite high as compared to other European countries.

France and Japan (and partly Italy), on the contrary, are examples of countries which adopted policies of direct price control in dealing with the supply side of the market. Moreover, price regulation was organized in such a way to protect the domestic industry from foreign competition and this thus offered little incentive to ambitious innovative strategies of firms (Thomas 1994, Henderson, Orsenigo and Pisano, 1999). The strategies in these national contexts would instead be to maximize returns under conditions of fairly stable products and prices.

In France, under the *Cadre de Prix* (subsequently called *Grille de Prix*), a fixed mark up was defined on each product, in principle taking into account the innovative characteristics of the drug, in order to enhance research. In practice, prices were simply held down and the system was used to favor quite openly French firms over foreign competitors.

Similar features can be found in the Japanese price control system, which divided products in four categories, according to their innovative potential, and allowed different levels of mark up based on price of similar products or, in absence of relevant information, on costs. The Ministry of Health and Welfare set the prices of all drugs, but using suggestions from the manufacturer based on the drug's efficacy and the prices of comparable products. Once fixed, however, the price was not been allowed to change over the life of the drug (Mitchell, Roehl and Slattery, 1995). Thus, whereas in many competitive contexts prices began to fall as a product matured, this was not the case in

Japan (as well as in France, that had a very similar system). Given that manufacturing costs often fall with cumulative experience, old drugs thus probably offered the highest profit margins to many Japanese companies, further curtailing the incentive to introduce new drugs. Moreover generally high prices in the domestic market provided Japanese pharmaceutical companies with ample profits and little incentive to expand overseas. Such system (coupled with product approval procedures that were quite lax for domestic companies but extremely harsh for foreign competitors<sup>5</sup>) has also been considered a form of industrial policy designed to protect the domestic industry. A very peculiar aspect of the system, moreover, was the “double” role of the physicians, who both prescribed and dispensed drugs to patients. They were able to negotiate discounts with the pharmaceutical manufacturers, and thus to “pocket” the difference between what they paid and the consumer did.

In both France and Japan, such controls have proven, according to many observers, as rather inefficient, in that they tended to reward incremental innovation and “me too” products. The low number of important NCE discovered, the small average size of firms in the industry and the limited degree of internationalization, are often considered as effects of such system.

#### *4.2. Procedures for product approval*

A second major change in regulation occurred as it concerns the procedures for product approval. It was again a drug disaster that pushed the US government to revise the drug safety control legislation. Quite interestingly, the fact took place in Europe, but the first response has been by the US. Starting from late 50s, the drug thalidomide was taken by pregnant European women to relieve morning sickness. Its use resulted in about 8000 deformed babies. The 1962 Kefauver-Harris Amendments strengthened FDA control power by extending it on clinical trials and development process, and by eliminating the limit of 60 days to approve a new drug. Moreover, the New Drug Application was preceded by an Investigational New Drug Application, to regulate the compounds progressing from pre-clinical to clinical testing.

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<sup>5</sup> Foreign companies had to carry clinical trials in Japan, under rules that specified that the drug should satisfy the special characteristics of the Japanese population.

The 1962 Amendments, actually, were originally intended to be the outcomes of the three years investigation, by the Kefauver committee, about the state of pharmaceutical industry in the US. The main line of attack to the industry was to show that firms were earning extra-profits, which only rarely were justified by huge investments in drug research: according to the committee, most molecules were just “manipulated”, and the drug that resulted were therapeutically similar to those already in the market: thus, much research could be eliminated without reducing the flow of therapeutically important drugs. The provision of efficacy controls, in addition to safety ones, was the result of such investigations. Specifically, the amendments required firms to provide substantial evidence of a new drug's efficacy based on “adequate and well controlled trials”. As a result, after 1962 the FDA (the Federal Drug Administration) shifted from a role as essentially an evaluator of evidence and research findings at the end of the R&D process to an active participant in the process itself (Grabowski and Vernon, 1983).

The favorable climate to enhance consumer protection as the main goal of a drug policy was witnessed, in the same year, by the Consumer Bill Of Rights, proclaimed by President John F. Kennedy in a message to Congress. Included were the right to safety, the right to be informed, the right to choose, and the right to be heard. In this climate a relatively wide consensus emerged on the relevance of safety controls and the role of public authority in the issue.

The reaction of the industry, and even of a large part of economic literature, was instead quite hostile to such reforms in the subsequent years. The stringency of the control procedure was seen as a major cause of the increase of costs of research, and of the slowdown of NCE discovery in the US. Moreover, it was contended that the time lag between molecule discovery and product approval reduced the effective patent duration, reducing incentives to innovate and hurting, first, smaller firms.

The effects of the Amendments on innovative activities and market structure have been the subject of considerable debate (see for instance Chien, 1979, Peltzman, 1974 and Comanor, 1986). They certainly led to:

- a) A large increases in the resources necessary to obtain approval of a new drug application (NDA),
- b) they probably caused sharp increases in both R&D costs and

- c) in the gestation times for new chemical entities (NCEs),
- d) along with large declines in the annual rate of NCE introduction for the industry as well as
- e) a lag in the introduction of significant new drugs therapies in the USA when compared to Germany and the UK.

However, the creation of a stringent drug approval process in the U.S. may have also helped create a strong competitive pressure favoring really innovative firm strategies. In fact, although the process of development and approval increased costs, it significantly increased barriers to imitation, even after patents expired, thereby penalizing the less innovative firms (Thomas, 1994). Thus, more recently, thanks also to deeper empirical analyses, it has been increasingly acknowledged that US firms have not lost their leading position in the discovery and production of “important” products, and have introduced some measure of technological opportunities depletion and shift in scientific paradigm to account for the actual slowdown in drug discovery in the seventies. It is a matter of fact, moreover, that after 1962 legislation no other tragedies occurred like thalidomide.

American 1962 legislation served as an important milestone in the evolution of the relevant legislation in Europe. The 1968 Medicines Act introduced in the UK a control system very similar to the American one, both for safety and efficacy control. Up to then, the system was on a voluntary basis: trials on drugs were conducted within the firms, and even after the thalidomide tragedy, the Committee on Safety of Drugs established for clinical trials scrutiny had no legal power. It comprised academic experts, supported by industry, and began its operations in 1964. The Committee on Safety of Medicines, which replaced the CSD after the 1968 reform, was intended as a formal government body, but depended anyway on the cooperation with firms, represented by the ABPI. This collaboration “resulted in the elitist collectivization of decision making on safety and efficacy levels” (Thomas, 1994). The multilateral collaboration between government, universities and the industry is a constant feature in British pharmaceuticals, and has long guaranteed a powerful position to the industry in such bargaining. Regarding safety control procedures, such collaboration led most firms to renounce to the complex appeal procedures to challenge government decision provided in the 1968 Act, and informal, “bargaining” solutions were preferred. The

growing complexity of the procedures, according to many observers, is then attributable more to the increasing complexity of the scientific paradigm. More generally, the reaction of the industry to the more stringent procedures has been “softer” than in the US, after a short phase of hostility following the formalization of the regulatory activity in 1968. As it was noted earlier, such “cooperation culture” has characterized even price control policies. As in the USA, the introduction of a tougher regulatory environment in the UK was followed by a sharp fall in the number of new drugs launched into Britain and a shakeout of firms in the industry. A number of smaller, weaker firms exited the market and the proportion of minor local products launched into the British market shrunk significantly. The strongest British firms gradually reoriented their R&D activities towards the development of more ambitious, global products (Thomas, 1994). Thus, stringent regulatory changes in the approval process increased the competitive pressures within the industry, particularly for the populations of firms either located in those countries or wishing to sell there. This type of change in government policy directed selection pressures to favor more innovative - and/or potentially more international – firms.

If the British industry has developed bargaining with public authorities “outside” the formal framework established in 1968, the reaction of German producer to the 1976 Medicines Act (Gesetz Über Der Verkehr Mit Arzneimitteln), even if not opposed to a system of licensing, was quite different. Before 1976, the Drug Act of 1961 required that firms just register their products with the Federal Health Authority, through a notification procedure. Such Authority was only endowed with the power to refuse products already known to be harmful. A very partial reform was enacted in 1964, as an answer to the thalidomide tragedy, requiring firms to give assurance about the correct procedure of safety tests conducted within the firms. The Medicines Act of 1976 was enacted by an SPD-FDP coalition in the regulatory and interventionist spirit of American and British earlier legislation on the issue. It should be noticed that both German and British systems have shown, in many fields, a preference for negotiated solution; nonetheless, the ways such bargaining have been conducted are substantially different in the two countries, and the case of drug safety and efficacy regulation is a good example. Contrary to British industry styles, German producers have tried to conduct negotiations on the application of 1976 Act “within” the new legal framework.

In the words of Hancher and Ruete, “Whereas their British counterparts have eschewed formal legal process [...], the German policy debate has been conducted [...] as an essentially legal debate, conducted in terms of the application of constitutional principles. [...] Law does not only provide the “technical” rules of society, [...] but also provides the language in which policy debates are often conducted” (Hancher and Ruete, 1987). This is witnessed, among other facts, by the huge number of recourses on appeal by German firms after 1976; the high rate of decisions in favor of the objector, in turn, shows the high bargaining power achieved by the industry.

According to many observers, the French system of drug licensing represents an interesting example on how regulation can be used as a protectionist policy. Registration of new drugs began quite early in France, in 1941, and the relative legislation required that only drugs produced in France, in laboratories owned by French pharmacists, could be sold on the domestic market. A reform in 1959, moreover, while relaxing the constraint of “domestic ownership”, gave the producer of a new drug the power to choose the expert to check the safety of the product<sup>6</sup>. The regulatory framework was not significantly modified after the thalidomide tragedy, and, in particular, efficacy controls were not explicitly added to the system.

In general, in Continental European countries, procedures for products approval were far less stringent than in the USA and Britain. This allowed the survival of smaller firms specialized in the commercialization of minor domestic products. In short, these firms became too protected relative to the changing international standards of their industry. One hypothesis is that one reason why U.S and British firms have fared better than other Continental European companies in the pharmaceutical industry in the third epoch is that they have faced relatively more stringent regulation, and they also been more internationally oriented (Thomas, 1994).

It is worth noting at this stage that the development of increasingly demanding and sophisticated clinical trials necessary for the approval of drugs had a further effect on a different domain, that would have become crucial in the following years, namely the pattern of industry-university relations. The design and implementation of

increasingly scientifically-based trials strengthened the interaction between companies and hospitals linked to medical schools. In effects, the main channel of interaction between pharmaceutical companies and universities had been so far teaching and the provision of skilled chemists and pharmacologists. Fundamental, basic scientific research played instead an important but less crucial role and only few firms surveyed systematically the developments taking place in the “new sciences”.

Finally, it has to be mentioned that drug approval procedures have been influenced in Europe by the evolution towards a single market by EU countries. The first attempt to harmonize national disciplines dates back to 1965, when a Directive required governments to set up a system of marketing authorizations for medicinal product. This represented a stimulus to reform national disciplines, along the lines exposed above, but did not provide any insight on how to harmonize the procedures. In other words, manufacturers who wished to market their medicines in different countries had to apply separately each country. The creation in 1975 of the Committee for Proprietary Medicinal Product, an advisory body charged with the task to review national procedures, and the establishment of a mutual recognition procedure in the same year, represent the first concrete step toward harmonization.

#### *4.3 Patents*

This second epoch, as already stated, was a golden age for the pharmaceutical industry. R&D spending literally exploded, which also led to a steady flow of new drugs. Drug innovation was a highly profitable activity for innovating firms during most of this period. Up to the early 1980s, double digit rates of growth in earnings and return-on-equity were the norm for most pharmaceutical companies, and the industry as a whole ranked among the most profitable in the United States and in Europe.

A number of structural factors supported the industry’s high average level of innovation and economic performance. One factor was the sheer magnitude of both the research opportunities and the unmet needs. In the early post-war years, there were many physical ailments and diseases for which no drugs had previously existed. In every major therapeutic category - from pain killers and anti-inflammatories to

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<sup>6</sup> In the same act, patent protection for pharmaceutical products was established. Moreover, recall that even the 1962 Amendments, in the US, required that at least one of the clinical studies must be conducted (PTO)

cardiovascular and central nervous system products - pharmaceutical companies faced an almost completely open field. Before the discovery of penicillin, very few drugs effectively cured diseases.

A second factor supporting the profitability of the industry was patent protection. Pharmaceuticals has historically been one of the few industries where patents provide solid protection against imitation (Klevorick et al. 1982). Firms wishing to succeed in pharmaceuticals through this type of blockbuster drug strategy had very strong incentives to be the first innovators, holding the patents. Because small variants in a molecule's structure can drastically alter its pharmacological properties, potential imitators often find it hard to work around the patent. Although other firms might undertake research in the same therapeutic class as an innovator, the probability of their finding another compound with the same therapeutic properties that did not infringe on the original patent could be quite small. Thus, being second could mean losing out - at least until patent expired and an alternative strategy of imitation could be carried out by some firms.

However, the scope and efficacy of patent protection has varied significantly across countries. The U.S have provided relatively strong patent protection in pharmaceuticals<sup>7</sup>. Yet, many other European countries, including Germany, France, Germany, Italy, Japan, Sweden and Switzerland did not offer protection for pharmaceutical products: only process technologies could be patented. Measures to strengthen patent laws in pharmaceuticals spread all over Europe during this period, but at a highly differentiated pace. France introduced product patents in 1960, Germany in 1968, Japan in 1976, Switzerland in 1977, Italy, Netherlands and Sweden in 1978, Canada and Denmark in 1983.

In many cases, as in Japan and Italy (and possibly France), the absence of product patent protection induced firms to avoid product R&D and to concentrate instead on finding novel processes for making existing molecules. In these countries,

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in the US, acting as a non-tariff barrier and favoring local innovative firms.

<sup>7</sup> Kingston (2000), moreover, recalls that a relevant feature explaining the strength of patent protection concerns the “post war” interpretation of “novelty” in patent granting decisions. Such interpretation shifted from “flash of creative genius” to “non obviousness” requirements, thus favoring those industries, like chemicals and pharmaceuticals, “in which inventions result from having a portfolio of research topics [...]. It is virtually certain that something patentable will be discovered within the portfolio [...]” (Kingston, 2000).

the development of me-too drugs, inventing around and getting licenses from other companies became the main research activity. The motivations for the absence of product patent protection were to be found in the desire to protect consumers from monopolistic pricing in a socially sensitive area and (less clearly and less explicitly) in the notion that patent on products might have stifled the diffusion of knowledge and new drugs. Perhaps more importantly, a further reason for not conceding product patents can be linked to a broader industrial policy, aimed to the development of a domestic drug sector and to the protection of the existing internal production (also through the establishment of subsidiaries of foreign multinationals).

In other cases, primarily Germany and Switzerland, but also in Sweden, the absence of product patent protection did not seem to produce such negative effects. Similarly, the reforms of patent laws do not appear to have had a visible and significant impact on the innovative capabilities of industries like the Italian or the Japanese one. If anything, it has been argued for example that it might have had a further negative effect, further weakening national industries mainly composed by generic producers (Scherer and Weisbursts, 1995).

In sum, the links between patent protection and innovative performance look less direct and than it is usually assumed. To be sure, it is highly likely that strong innovating companies, active in the whole world, have used other instruments to extract profits from their innovations. For example, German and Swiss companies have certainly actively patented their drugs in the USA in order to penetrate that market. Similarly, advertising, direct foreign investment and licensing are also likely to have performed as powerful mechanisms for appropriability, especially in an era when generic competition was not as strong as it is today<sup>8</sup>.

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<sup>8</sup> The organizational capabilities developed by the larger pharmaceutical firms may also have acted as a mechanism of appropriability. Consider, for example, the process of random screening, i.e. the fundamental procedure governing drug discovery in this era of the industry. As an organizational process, random screening was anything but random. Over time, early entrants into the pharmaceutical industry developed highly disciplined processes for carrying out mass screening programs, which require systematic search strategies as well as handling large amounts of data in a sophisticated manner. Because random screening capabilities were based on internal to the firm organizational processes and tacit skills, they were difficult for potential entrants to imitate and thus became a source of first-mover advantage. In addition, for random screening, spillovers of knowledge between firms were relatively small, so firms already having an advantage could maintain that advantage over time as compared to firms wishing to enter. Since these firms essentially rely on the law of large numbers, there is relatively little to be learned from the competition, but much to be learned from large scale screening in-house. Each firm needed  
(PTO)

More generally, these observations suggest the conjecture that strong patent laws do indeed confer an advantage to innovators, but they are not enough to promote innovation in contexts where innovative capabilities are low or missing altogether. Similarly, high degrees of appropriability are likely to be particularly important for sustaining innovation in highly innovative and competitive environments, rather than in situations where little innovation takes place anyhow. In other words, patents magnify the incentives to innovate, but do not create them, in the absence of the competencies that make innovation possible in the first place. Thus, strong incentives can create virtuous circles when they are coupled with strong competencies, but they might be ineffective and even dangerous when the latter are insufficient. The opposite is also likely to be true: competencies without incentives are probably bound to be underutilized and wasted. Incentive and competencies are best seen as co-evolving. Moreover, patent laws can be seen, just like safety and price/cost control policies, as the result of the interaction of different and potentially conflicting objectives.

#### *4.4 Biomedical research: funding and organization*

A third factor behind the growth of pharmaceuticals in this second epoch concerned fundamental research and industry-university relations. The upsurge in public funding of biomedical research was doubtlessly a tremendously important engine of growth for the pharmaceutical industry, providing better understanding of the causes of diseases and of their potential cures and hence new opportunities for innovation.

Funding of biomedical research can be therefore considered as the supply of a public good (or some sort of a subsidy) for the industry. As such, policies governing the funding and organization of basic research enter into the panoply of the governments actions that directly or indirectly, consciously or unconsciously affect the innovativeness and the overall performance of the industry.

Before the war, the linkages between the pharmaceutical industry and basic scientific research had certainly been present (Galambos and Sewell, 1995; Lamoreaux and Galambos, 1996; Galambos and Sturchio 1997), but were not systematic nor widespread.

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access to the appropriate information infrastructure for their therapeutic areas (Henderson, Orsenigo and Pisano, 1999).

In this second era, this situation started to change and paved the way for the subsequent explosion of university-industry relations in the Eighties. It was in these years that the American research system started to gain an absolute leadership in scientific research. Before the war young Americans interested in starting a scientific career went to Europe to specialize and to get access to leading edge science, while in the post-war period the situation quickly reversed (see among others, Rosenberg and Nelson, 1994). With the war, many good European scientists relocated to the USA.

In the specific case of biomedical research, in this period, linkages with universities and basic research consolidated and started to change their nature, both as a consequence of the increase in public spending for biomedical research and to the introduction of more demanding procedures for products approval. From the perspective of pharmaceutical firms, they needed access to systematic clinical testing, which was usually organized through the medical research system as well as to fundamental scientific results which increased the biological understanding of diseases, drugs, and cures. Increasing biological understanding should increase the efficiency of the firm's own internal R&D search processes as well as form the types of collaboration necessary to monitor external knowledge developments.

Nearly every government in the developed world supports publicly funded health related research, but there are very significant differences across countries in both the level of support offered, in the ways in which it was spent and in the emphasis attributed to the potential products that might have been generated by such research.

While the potential benefits of this research efforts for public health and the production of new drugs were quite obviously emphasized by almost all governments, there were large differences across countries in the consideration of the effects that public research might have had for the industry. Nowhere public funding for biomedical research was ever openly advocated as something that could have a direct impact on the competitiveness of the industry. However, in the USA and partly in the UK the awareness that such research had to link with the production of new drugs and hence with the commercial world was relatively clear. Take the extreme case of molecular biology. In the USA and in the UK support to molecular biology was given irrespective of any practical consideration of the potential immediate benefits in terms of health care. Conversely, in other countries, primarily France, this connection was very explicit.

Yet, especially in the early post-war years, molecular biology research was much more linked to biomedical research in hospitals and medical schools in the USA and in the UK than in other European countries, where it had closer relations with the physicists and with more conventional biology institutes (Morange, 1994; Krige, 2000, Strasser 2000, de Chadarevian 2000).3--

In the US, public spending on health related research took off soon after the second world war. Public funding of biomedical research also increased dramatically in Europe in the post-war period, although total European spending did not approach American levels (and, after the end of the war, UK government expenditures on biomedical research were significantly lower than in most other OECD countries (Thomas, 1994). There is little question that the sheer amount of resources devoted to biomedical research in the USA in the post-war era goes a long way to explain the American leadership in life sciences. The American money was also more concentrated to centers of excellence, thereby providing critical mass of researchers - while also the sheer diversity of the American research system allowed many alternatives to be tested early on.

Both qualitative and quantitative evidence suggests that this spending has had a significant effect on the productivity of those large US firms that were able to take advantage of it (Ward, Dranove, 1995; Cockburn, Henderson, 1996; Maxwell, Eckhardt, 1990). As a consequence - and despite the existence of centers of absolute excellence - the overall quantity and quality of scientific research lagged behind in Europe. In turn, this created a vicious circle, with a significant drain of human and financial resources from Europe to the USA, which contributed to further strengthen the American advantage.

In addition, the institutional structure of biomedical research evolved quite differently in Continental Europe as opposed to the USA (and partly to the UK). By institutional structure, we mean how the flow, level, and direction of research resources are organized - where this in turn is assumed to affect the science performed in the respective national contexts. First, the structure of the funding system and the strategies of the funding agencies are crucially important to influence research results, and these differ between USA and Europe. In the USA, most of the funding was administered through the NIH, although a significant fraction went to universities and an important

fraction of the support went towards basic or fundamental science that is widely disseminated through publication in the refereed literature. Still, the orientation towards health was implicit when not explicit. Moreover, the American system has been characterized by a variety of sources of funding and selection mechanisms, which complemented the role of the NIH and acted – always starting from scientific excellence - according to different allocative principles. This approach introduced some form of competition between financiers, and so it allowed diversity to be explored, while also maintaining this emphasis on quality, fundamental science. This enabled institutional flexibility.

In Europe, funding has been administered mainly at the national level, with strongly differentiated approaches and wide differences across countries. This is likely to have hindered the development of a critical mass of research in key fields, especially in smaller countries. Countries may also focus on non-critical research. In many cases, resources have either been dispersed among a large number of “small” laboratories, or have been excessively concentrated in the few available centers of excellence<sup>9</sup>. It is widely recognized that the absolute size and the higher degree of integration of the American research system, as opposed to the fragmented collection of national systems in Europe constituted a fundamental difference between the research systems.

In addition to differences in the allocatory principles for scientific research, the institutional structure of biomedical research itself evolved quite different in Continental Europe as opposed to the USA and the UK. In particular, biomedical research in Europe was much less integrated with teaching and within universities in Continental Europe, with the result that medical research has tended to have a more marginal role compared to patient care. In other words, this organizational structures - combined with pressures from cost containment in welfare states - led to an emphasis to treat patients, not learn more about them.

The relevance of the research-teaching nexus in favoring high quality scientific research and its integration with industrial research can hardly be underrated. In particular, the diffusion of molecular biology into general training in many European countries is a relatively recent phenomenon as compared to the USA and it has only

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<sup>9</sup> In more recent years, funding coming from the various European programs has only partially changed the situation (see Pavitt, 1998).

recently become a standard part of the curriculum of pharmacologists, pathologists and medical consultants. In Europe, research tended to be confined into highly specialized laboratories in universities and especially in public research centers, with little interaction with teaching, medical practice and, a fortiori, with industrial research.

Different patterns are visible in different European national contexts. In the UK biomedical research was conducted mainly in the medical schools. The Department of Health and the Department for Education and Science - particularly through the Medical Research Council (MRC) - have been the main funding agencies. Later, private foundations such as the Wellcome Trust have also emerged as major sources of funding. The MRC funded internal and especially external research at universities (approximately two thirds of the total), a much larger proportion than in France. More generally, around the NHS (which was extended to the whole population in 1948) a dense web of close interactions was created between academic research, companies and medical practice. As Thomas (1994) discusses, this system was strongly science-oriented, elitist and above all promoted the informal sharing of control among government the medical profession and industry.

In France, in contrast, biomedical research was largely performed by CNRS and especially INSERM, which was founded in 1964 to strengthen basic research in the field. In Germany the main actors in biomedical research were the DFG (Deutsche Forschungsgemeinschaft) and the MPG (Max Planck Gesellschaft). DFG funded external research, while MPG received funds from the federal and state governments for conducting essentially internal research. After 1972 the newly founded Ministry of Science and Technology (BMFT) emerged as a major actor, sparking sometimes bitter conflict with the other agencies and with universities, particularly with the so called "big science centers" which carry out independent research in a limited number of fields.

Other, perhaps less tangible, factors have interacted in Continental Europe to create an environment which taken as a total together not only produced less science of generally lower quality but also one in which science was far less integrated with medical practice and industrial concerns.

First of all, in Continental Europe within the medical profession, in general science did not confer the same status that it did within the Anglo-Saxon countries.

Traditionally the medical profession in Continental Europe has had less scientific preparation than is typical in either the UK or the USA. Medical training and practice have focused less on scientific methods per se than on the ability to use the results of research (Ben-David, 1977, Clark, 1994, Thomas, 1994). Moreover PhDs in the relevant scientific disciplines have been far less professionally-orientated than in the USA or England (Ben-David, 1977; Braun, 1994). Partly as a consequence, medically oriented research within universities has tended to have a marginal role as compared to patient care. Historically the incentives to engage in patient care at the expense of research have been very high: France or Germany have only recently implemented a full time system designed to free clinicians from their financial ties to patient-related activities. The organizational structure of medical schools has been such as to reinforce this effect. In Continental Europe medical schools and hospitals are part of a single organizational entity, whereas in the USA and the UK they are autonomous actors, which periodically negotiate as to the character of their association. In principle, the European system should have a number of advantages with respect to research and teaching. In practice, the European system has tended to have negative consequences as patient care has tended to absorb the largest fraction of time and financial resources. In these systems, resources are not usually target to specific activities and given the difficulty of quantifying their cost, even when a fraction of the subsidies provided by the government are supposed to be used for purposes of research and teaching, patient care easily makes inroads into these supposedly "protected" resources (Braun, 1994).

The weakness of the research function within hospitals in Continental Europe was one of the reasons why the decision was made to concentrate biomedical research in national laboratories rather than in medical schools as happened in the US and the UK. This should provide separate centers of excellence within research. However it has often been suggested that the separation of the research from daily medical practice had a negative effect on its quality and especially on the rate at which it diffused into the medical community (Braun, 1994, Thomas, 1994).

#### *4.5 A Reprise*

In sum, in this second epoch, direct and indirect regulation, like patent legislation, procedures for product approval and price regulation, as well as the

development of the Welfare State and the soaring funding of biomedical research had an enormous impact on the growth of the pharmaceutical industry.

In some cases, government actions ended up favoring the more innovation-oriented firms, in other cases the marketing-oriented companies, and even the less efficient smaller firms mainly operating on domestic, protected markets. It is hard to establish any specific direction of causation – let alone a linear relation - between one particular institutional feature, the nature of competition and the degree of innovativeness. For example, it is by no means clear that price regulation or weak patent protection had always a negative and discernible effect on the incentives and the ability to innovate. For example, the British system of price regulation worked pretty well in inducing a virtuous circle between competition, incentives and innovative capabilities. Rather, specific combinations of these variables conjured to produce particular competitive environments favoring the adoption of innovative strategies. Moreover, it is worth noting that many of these institutional arrangements were not devised with the explicit aim of favoring innovation or even industrial prowess. Rather, they resulted from different purposes - like social policies or science policies- but ended up – after sometimes quite prolonged periods of time - bearing important consequences on the capacity and willingness to innovate.

## ***5. The Age of Science and Cost Containment***

### *5.1 Changes in technology, demand and regulation*

The third epoch in our characterization runs from the mid-Seventies through the present. This epoch started with the advent of the knowledge revolution to pharmaceuticals associated with molecular biology as well as shifts in the nature of demand.

Beginning in the early seventies, the industry began to benefit more directly from the explosion in public funding for health related research that followed the war. The development of new knowledge bases in modern biotechnology as well as in fundamental biological and medical areas transformed radically the cognitive and organizational nature of the processes of learning and discovery. Science became a

fundamental competitive asset for companies and this led to a radical transformation of the procedures of drug discovery within firms (Henderson, 1994) and of the whole organization of the industry, with the appearance of the new biotechnology firms, the emergence of a dense network of collaborative research between large corporations and new biotechnology companies, an increasing involvement of universities in the commercial activities. This revolution changed also quite drastically the competitiveness of individual firms and national industries. Europe, from a position of dominance, certainly lagged behind the USA (Orsenigo, 1989, Gambardella, 1995, Henderson, Orsenigo and Pisano, 1999; Gambardella, Orsenigo and Pammolli, 2000; McKelvey and Orsenigo, 2001).

The very rise of the “new” pharmaceutical industry was deeply influenced by the regulatory environments prevailing in the various countries as well as by the levels and forms of organization of scientific research. It also triggered major changes in regulation, especially as intellectual property rights legislation and practice are concerned.

Contextually to the changes in the technological regime, another series of important transformations were taking place at the level of the regulation and of the demand side of the industry. They concern mainly changes in attitudes and legislation towards pricing, driven essentially by the emergence of cost-containment considerations. Especially in the USA these developments were marked by the appearance of new actors - the managed care organizations - which induced a deep transformation in the structure of the distribution system and more generally in the demand behavior of the consumers (purchasers), by radically strengthening their bargaining position vis-a-vis producers and integrating previously fragmented purchasing decisions. To these, one must consider increasing stringency of the processes of required for the approval of products and the impulses given to the diffusion of generics. In both cases, the “regulatory revolution” interacted with the “scientific revolution” in shaping the sectoral system of innovation. Once again, the patterns of development of the sectoral system were quite different across countries.

#### 5.1.1 Product approval procedures and agencies

During the Eighties, the trends initiated in the previous period towards increasingly stringent controls on product approvals requirements continued and, if anything strengthened, especially in Europe.

In particular, the evolution towards a single market by EU countries has involved attempts towards the harmonization of national laws and approaches towards drug approval procedures. The creation in 1975 of the Committee for Proprietary Medicinal Product, an advisory body charged with the task to review national procedures, and the establishment of a mutual recognition procedure in the same year, were reinforced, in 1995, by the definition of an arbitration procedure, managed by CPMP. Under this system, the evaluation is made by one state and other states are required to automatically approve the product in their territories. Any member state has still the option to refer the matter to the CPMP for arbitration. In the same year a parallel procedure, centralized at community level, came into effect, and is now compulsory for biotech drugs. Such central application permits a manufacturer to refer directly to a single Agency, the EMEA (European Medicines Evaluation Agency), headquartered in London. The EMEA refers to the CPMP, and final decision rests with the European Commission. It should be noticed that the EMEA lacks any enforcement power, which remains at national level and in the hands of the Commission. The agency, unlike, e.g., the FDA, has a coordinating role, and its activity is one of “pooling the scientific expertise of Member states in order to ensure a high degree of protection for public health, ensuring free movement of pharmaceuticals, and making certain that Europeans have access to new generations of medicinal products” (European Commission, 2001).

According to some authors, paradoxically, such “weakness” could represent an advantage for the efficacy of EMEA’s activity. On one side, the light structure of coordinator of scientific activity in single member states may enhance scientific knowledge exchange (for example, because EMEA is able to choose reviewers from a very large pool at Continental level), without a heavy (and slow in approval process) bureaucratic structure on the FDA model. On the other, the coexistence of a centralized and a de-centralized system (mutual recognition) provides competition and an incentive to efficiency. An assessment of the validity of the double system in Europe is probably premature. It is a matter of fact that single member states maintain a great power in the

process, and the lack of legal mandate and enforcement power of EMEA does not make it, at least in the short term, a credible substitute of national authorities.

In fact, in the USA, in recent years a new line of attack to safety control procedures has emerged: it is the organization of control agencies, especially the FDA, to raise criticism for its bureaucratic structure and the lobbying activities it exerts and that is addressed to it by different pressure groups. The FDA, in other words, enjoys a large autonomy and large enforcement power, making it a key actor in the evolution and performance of the US industry. Autonomy and discretion, however, does not mean complete independence from a diversified constituency including the administration and parliament, the industry, and consumers. Many studies have tried to highlight the different pressures the FDA is subjected to, and the different degree of autonomy it can exert in different situations. It is common opinion that, if some form of democratic control is necessary (and the election of FDA chief by the president with Senate approval from 1989 is an expression of this feeling), certain autonomy is almost inevitable, given also the increasing complexity of the scientific and technological paradigm. It is interesting to notice that the most famous scandal in the recent FDA history exploded in 1988/1989, and concerned a case of corruption for the approval of generic product, the kind of drugs on which, according to empirical analyses, the FDA is more subject to external influence and has thus less autonomy, in terms, for example, of resource and staff allocation decisions. This case, moreover, stimulated an intense debate among public opinion on the role of the agency, and involved many people even in complex debates, to an extent unknown in Europe.

Another relevant attempt to harmonize product approval disciplines is in progress between the US and Japan, within the “Enhanced initiative on deregulation and competition policy”. Such program, according to many authors, will require a drastic re-thinking of the Japanese system of product approval, established in the 50s, and now described as a mix of protectionism, opacity in the decision processes, a lack of scientific competence. The system, managed by the Ministry of Health and Welfare, is taken as softer than European and American ones, in that it provides a lesser number of trials and its tests are often conducted by scientists having relations with involved firms. The structure, further, can rely on fewer personnel. Up to recent year, test data from experiments in other countries were not allowed to be considered in the domestic

product approval process, and even information about undesired effects of some drugs in other countries was taken into account with considerable delay. Thalidomide kept being sold several months after the scandal emerged in Europe, and this caused more than 300 cases of birth defects. Later, prescription on the use of heated blood were applied after some time, causing an abnormal diffusion of HIV among hemophiliac people. According to Pollac (1995), these facts also show the paternalism of the Japanese health system, as people receive little or no explanation about the therapy they are subjected to<sup>10</sup>.

### 5.1.2. Cost containment

The main institutional change, however, was in this period the emergence of cost containment policies.

In the OECD countries, the real total pharmaceutical expenditure (in constant terms) grew at an average yearly rate of 3.5% in the 1980s and of 4.6% from 1990 to 1996 (Jacobzone 2000). This growth was determined partly by rising income. However, pharmaceutical expenditure grew on average 1.5% more than GDP growth since the 1970s. Thus, other factors, related to increasing prices of drugs and aging population, contributed also to the rise of expenditures. In any case, increasing pharmaceutical expenditure implied also growing pressure on public outlays. In a period characterized by mounting concerns over budget deficits and – more generally – over the extension of public intervention in the economy, pharmaceutical expenditures became a primary target for expense reduction. On the other hand, health care has become to be increasingly perceived as a fundamental human right and/or in some cases as a public good<sup>11</sup>. Thus, decreasing public coverage of pharmaceutical expenditure is sometimes

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<sup>10</sup> It is worth recalling, talking about harmonization, the activity of the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, established as a joint regulatory/industry project in 1990 by representatives of the regulatory agencies and industry associations of Europe, Japan and the USA and supposed to be an international forum of discussion about different topic about the issue of regulation. To date, ICH has promoted a number of meetings and workshops, and produced many documents and guidelines, achieving a large consensus in the scientific community and some “hearing” by policy makers.

<sup>11</sup> Take for example the argument in favour of tougher – and prohibitionists – measures against smoke. Often, part of it is based on the notion that smoke is a public evil, because smokers harm non-smokers and because curing smokers is extremely expensive for the society. Moreover, a prohibitionist attitude is also justified on the grounds that smokers are not smart enough to behave in such a way to maximize their welfare. However, it is interesting to notice that sometimes the very same proponents of a tougher stance would strongly oppose the notions that individual health is a public good, worth of being subsidized by  
(PTO)

seen as a threat to a fundamental and consolidated right and - to the extent that it hits especially the poorer fractions of the population – to a basic principle of equity. On these ground, in some countries, like Sweden, there were even suggestions to nationalize the pharmaceutical industry, in the early Eighties. On the other hand, the inefficiencies are stressed that are generated by excessive public coverage of drug expenditure (e.g. excessive consumption of drugs) and by command-and control measures like the various forms of price controls. As a consequence, in many instances, the regulation of the market for drugs has become also a symbolic issue within the debate over the “downsizing” of the Welfare State.

Actually, the approaches towards cost-containment differ substantially across countries and over time and reflect the specific histories and institutional settings of each countries. However, a common trend is discernible towards the increasing use of policies aiming at intervening on the demand side of the market to make patients and health providers (doctors and pharmacists) more price-conscious and more price-sensitive (Mossialos, 1997), without or irrespective of direct price controls. This type of measures include various forms of co-payment, the use of formularies, the development of the market for generics and other interventions attempting at changing the behavior of providers through financial incentives and penalties (e.g. introduction of budgets for GPs, payment of doctors on a capitation basis, etc..). Moreover, price controls seem to be moving away from cost-plus based systems and slowly converging towards systems of reference pricing.

Regulation intervenes directly on the demand of patients, through different schemes of cost sharing (proportionality to the final price, fixed charges, etc...), thus increasing the price sensitivity of consumers, both in order to reduce public expenditures and to limit over-consumption of drugs.

A recent form of cost sharing is the reference price system, in which reimbursement is limited to a certain level, e.g. the average or the lowest price of “bio-equivalent” drugs, including generics. Generic substitution meets broad agreements, and now many countries try to promote the diffusion of non-branded drugs. Germany, the European country with highest average drug prices and one of the first to implement

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the state and that individuals are unable to evaluate the benefits stemming from competing drugs (and therefore that some form of price control might be justifiable in terms of informational asymmetries).

generic substitution policies, now experiences the largest diffusion of non branded drugs in Europe.

Another intervention pattern has been to influence the prescribing behavior of physicians; there are many examples of such policies, implemented both by public authorities in Europe and by private managed care institutions in the US. They range from the definition of guidelines to budget fixing, either at individual or more aggregate (e. g., per region or per medical association) level.

Such policies have proved to be relatively effective, at least in the short run, in containing expenditure growth. Nonetheless, some authors have exposed caveats from at least two points of view. On one side, it has been noticed that these interventions, especially the ones directed to patients, are typically regressive, as wealthier people can afford integration to the common health insurance, thus covering the full drug price. Moreover, policies like reference pricing require an adequate diffusion of information among consumers, in order to give them an effective freedom of choice. More generally, a problem arises whenever the objective of providing the best cures for the highest share of population is taken as a primary goal. Recall that pharmaceuticals have long been considered as merit goods, or goods for which price signals can actually distort decision from the “optimal” choice. Finally, consumers’ and, even more, physicians’ behavior show strong habits components (reinforced by the advertising strategies of companies), which to date have not been adequately analyzed but that, anyway, reduce the effects of economic incentives (Jacobzone, 2000).

A completely different set of objection is based on the fact that, if such policies have some impact on expenditures in the short run, expenditure patterns tend to rapidly return on the long run trend.

Within this broad context of shifting attitudes towards regulation and despite some deep and important changes (e.g. the UK in the Thatcher era), policy-making maintains in each country strong degrees of inertia and continuity. In other words, policy making follows routines and trajectories that partly depend on the intrinsic rigidity of the constitutional and administrative systems and partly on how public agencies are used to think and do. In particular, price controls are still in place and have been reinforced, although they are gradually converging to some form of reference pricing mechanisms.

In the USA, cost containment has been pursued without direct price controls. Indeed, we already observed that criticisms about the high price of drugs arose already in the late 1950s and 1960s. The Kefauver Committee denounced the disproportionate profit margins that US drug firms were earning, thanks to high prices and much lower costs than what was publicized. The main concern of the Committee was consumer protection, even in terms of affordable access to medicines, rather than excessive public expenditure. The issue was revived in the Nineties by the Clinton administration as part of an attempt to introduce universal health care coverage in a country where 37m people do not have any form of insurance and 22m have insufficient coverage. Within this context, it was proposed to control drug expenditures, given that the governments is anyway a huge drug buyer, with Medicare and Medicaid programs accounting for more than 40% of healthcare expenditures. Clinton's proposals, like the creation of regional purchasing cooperatives (Health Alliances), the introduction of employers mandate, and "cross-financing" through increases in taxes on alcohol and tobacco, were harshly criticized, and only a small part of the proposed reforms have been enforced. The opponents' arguments rely mainly one two types of arguments. The first is that higher prices allow firms to reinvest in research of new products, and price controls may hinder a country's innovative potential. According to some observers, countries in which there is some form of price control actually free ride on US research activity. Second, it is argued that price controls are an inefficient, ineffective and distorsive instrument for purposes of cost-containment. While the argument is quite complex, it essentially relies on the observation that reductions in price goes along an increase in the demand, and then that the demand is not completely inelastic (especially if there are cost-sharing measures); such demand, moreover, tends to shift towards "unnecessary" products.

While the US market is still on the surface free of any price control, indirect measures have been adopted in the last 20 years. The 1984 Waxman-Hatch Act significantly reduced the safety control procedures for generic drug bio-equivalent to branded products and allow pharmacist to sell equivalent generics instead of branded products prescribed by doctors<sup>12</sup>. Today generics are estimated to account for more than 50% of drug prescribed (in volume. See McIntyre, 1999). Moreover, the rise and

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<sup>12</sup> The same Act provided a "restoration" of patent duration to take into account delays in the approval process.

diffusion of the managed care organizations, like Health Management Organizations (HMOs), Preferred Providers Organizations (PPOs), mail-order pharmaceutical organizations and Pharmaceutical Benefit Management (PBMs) companies, that now dominate the US healthcare market, is considered as the most effective device for limiting the prices of drugs, given their bargaining power and the inducement they introduce to cost-conscious behavior by prescribing doctors. Actually, managed care organizations have changed profoundly the structure of distribution and demand in the USA and they have become crucial players in the sectoral system of innovation. The growing relevance of these actors induced also processes of vertical integration, through the acquisition of PBMs by large pharma corporations (e.g. Merck acquired Medco Containment in 1993 and SmithKline bought Diversified Pharmaceutical Services in 1994).

In Europe, cost containment policies took different routes, again because - contrary to the US case - the State is the largest customer of drugs and partly because of much stronger resistance to measures that might be perceived as weakening a fundamental function of the of the Welfare State.

In the UK, a relevant breakthrough in the system defined by the Pharmaceutical Price Regulation Scheme, occurred in early 80's, when the government, under the pressure of cost increasing, unilaterally defined in 1983 a limited list of drugs for which there would be no reimbursement. The unilateral and "institutional" way the decision was taken generated tension between the government and the industry, who accused a violation of the (implicit) rules of the game. Each firm conducted bargaining on the definition of the limited list quite independently, and some of them reacted by leaving the British market. However, government-industry relations were restored quite quickly. UK drug prices are on European average. In addition to the "direct" intervention on price definition, in the UK increasingly tight drug budgets for physicians have been implemented. It has been noticed, although the evidence remains inadequate, that British and North European doctors appear to be more cost-conscious in their prescription patterns than doctors from other countries, with lower rates of prescription of more expensive and potentially unnecessary drugs.

In Germany too, the slowdown of growth and, more importantly, the reunification process, put on the table the problem of soaring health costs. The adopted

measures concentrated on interventions aimed at rising price consciousness and sensitivity, without direct price controls (except a price freeze in 1994), continuing the stance consistently pursued in the past. Reforms in the early 1990s introduced budgets for controlling doctors prescription behavior, increased co-payments and widened the reliance on reference prices in reimbursements. According to some observers, the drug policy style is linked to the government features and the relationships between industry and political power. In particular, Germany has experienced the prevalence of coalition governments, in which the Liberal Party has often enjoyed a disproportionate power with respect to its dimension; this party has long had very strict relationships with drug manufacturers, defending their interests in the policymaking process. Moreover, the division of responsibility between the federal, state and local level of government has multiplied influence channels for the industry and has led to a sort of government “immobilism” (Macmillan and Turner, 1987).

In France, an agreement between government and industry was reached in 1994 that allows for more pricing freedom in exchange for government control on total spending. A target growth rate is established for general pharmaceutical expenditures and then a negotiation takes place with each manufacturer that fixes a specific limit on the firm’s total revenue growth. On the other hand, patients co-payments remain only nominal, as a consequence of the increasing coverage with supplementary insurance that has to reach 100% of the population.

In Italy too reference pricing mechanisms, increasing patients’ co-payment and global budgets for doctors have been introduced since 1993, after a major scandal involving bribes to the price review board.

In sum, despite these changes, some basic features of the national systems of regulation of prices and demand continue to characterize individual European countries. For example, Italy, France, Greece, Belgium and Spain and to a lesser extent Sweden continue to implement strict price controls, while Germany and Switzerland have a much less stringent attitude. The former group of countries continues to be characterized by relatively low prices and Germany by high prices. Yet, price levels in France are now at an intermediate level, similar to the British ones. Moreover, public coverage of pharmaceutical expenditure has been severely decreasing in Italy in the

Nineties and has been actually increasing in Norway and Ireland but also in the USA, Canada, Switzerland, France, Greece and to a lesser extent Sweden (Jacobzone, 2000).

However, assessing the impact of the various policy measures on pharmaceutical expenditure, on the access to drugs by different segments of the population remains extremely difficult and controversial. In general, there seems to be some consensus on the fact that all these measures did little to curb pharmaceutical expenditure, and at best they have prevented it from soaring. On the other hand, it seems to be increasingly acknowledged that strong competition within domestic markets and exposure to international competition is conducive to a better innovative performance and higher levels of competitiveness. Despite the “invasion” of generic drugs and the more competitive environment that firms face within the domestic market, R&D resources and innovative outcome certainly does not seem to deteriorate in the US, which has consolidated in the 80s its leadership in the world drug sector. Perhaps even more important, excessive reliance on command and control instruments appears to protect the less efficient segments of the industry (Gambardella, Orsenigo and Pammolli, 2000) rather than hindering innovation *per se*.

In any case, the analysis of regulation and of the evolution of demand illustrates once again the conflicts and continuing changes that characterize pharmaceuticals. The expansion of the Welfare State contributed to the explosion of pharmaceutical expenses and led to cost containment policies. Objectives of equity are in a continuous tension with economic static and dynamic efficiency and claims on either side that no trade-off actually exists are at best difficult to prove theoretically, let alone empirically. Different goals are attributed shifting importance over time and different arguments and rationales are used to support or contradict particular policy attitudes. Thus, as equity and information asymmetries used to be the main motive for policy intervention, now cost containment has become the main issue. Promotion of national industries remains an important factor shaping policies, perhaps even more explicitly than in the past, but in a profoundly different vision of the sources of competitiveness. Such tensions and conflicting goals result in frequent changes in legislation, adjustments and sometimes proposals of radical reforms, never finding an equilibrium.

### *5.3 Industry-University relations and Intellectual Property Rights*

As mentioned earlier, “the molecular biology” revolution radically transformed the ways research is organized and conducted and the structure of the industry. In particular, the development of the “biotechnology industry” in the USA rested on the concomitant growth of series of supporting organizations, institutions and legislation which are now perceived as defining the distinct character of the “American way” to innovation, at least in high-tech industries. This system is organized around the nexus between academia, institutions governing property rights and venture capital (Mowery and Rosenberg, 1999). Developments in legislation about intellectual property rights had in particular a very important influence in shaping industry evolution.

The key role acquired by scientific knowledge for technological innovation manifested itself in an unprecedented intensification of both industry-university ties and in the direct involvement of academic institutions and scientists in commercial activities.

Both phenomena are certainly not new in the USA. As documented by Rosenberg and Nelson (1993), Etzkowitz (1999), Mowery et al (2000) among others, the very development of the US academic system was tightly linked to industry needs. Some universities have been engaged in patenting and even in the promotion of spin-offs ever since the beginning of the 20th century.

However, since the mid-Seventies, the drive towards an increasing commercialization of the results of research accelerated dramatically and took a variety of forms. Universities’ patenting and licensing activities started to soar. The number of universities having established Offices for Technology Management also increased from 25 in 1980 to 200 in 1990 (Cohen, Florida and Goe 1994). As discussed before, the creation of spin-offs became a distinct and crucial phenomenon of the American academic system. Increasingly, universities were assuming and were asked to assume the role of direct engines of (local) economic growth.

The emergence of the entrepreneurial university and the specific forms this process took in the USA are strictly linked to some basic characteristics of the US academic system. Not only, as just mentioned, the American universities were traditionally highly responsive to the needs of the local communities and industries. Also the organization of research and teaching had characteristics that facilitated both

the production of high quality research and high degrees of mobility between academia and the commercial world.

Specifically, in the USA (and in Great Britain) departments have long been the main organizational entities as opposed to the European institutes, dominated by a single professor, far less interdisciplinary in nature and with feudal-like career paths. Moreover, in the USA high degrees of integration between teaching and learning have been achieved through the sharp separation between undergraduate and post-graduate levels. The creation of research-oriented post-graduate studies entailed, in fact, a number of important consequences. In particular, post-graduate students are typically exposed and trained to the practice of scientific research within research teams composed by students and professors within departmental organizations. This arrangement does not only tend to free resources for scientific research, but provides also a fundamental experience in participating to and managing relatively complex organizations. In other words, it constitutes an essential source for the development of organizational capabilities. Moreover, the career of young research scientists after graduate studies has – under various perspectives - entrepreneurial characteristics. For instance, post-docs have to raise funds for their own research in a highly competitive environment, where performance is judged on the basis of a track record and the ability to set an independent research agenda (Gittelman, 2000). Finally, graduate students joining the industrial world after the completion of their studies constitute an essential source of skilled demand for academic research.

In Continental Europe, the integration of teaching with research has progressed far less than in the USA (and to some extent than in the UK). Clearly, enormous differences in education systems, especially on the higher education level, exist across Continental European countries and they certainly should not be overlooked. For example, as it was mentioned previously, in France, universities have never been the main center of both scientific research - which has been essentially conducted within the national laboratories and co-ordinated by the CNRS (National Center for Scientific Research) - and the education of the elites - monopolized by the system of the *grandes*

*écoles*. In Germany, the “institute” – dominated by an individual professor – has been the main organizational unit co-ordinating teaching and research<sup>13</sup>.

Despite these enormous differences, the structure of the academic systems of many European countries shares some important common features, as compared to the Anglo-Saxon systems. Ph.Ds are a relatively recent innovation in many Continental European countries and they remain far less professionally orientated than in the U.S.A. Departmental structures are also relatively new and in many cases institutes continue to be a very important organizational entity. In general, research has tended to be far more removed from teaching than in the USA. And in fact, in many Continental European countries, research has been to a large extent separated from universities and concentrated in specialized institutions. At the cost of oversimplification, in Europe a model has been emerging based on high degrees of division of labor and specialization between teaching and research institutions, whereas in the USA the dominant model has been an integrated one.

It is possible to speculate that this separation might have had negative effects on both the quality of research and on the ability of academic institutions to interact with industry. Integration of research and teaching and collaboration with industry has been relatively more developed and frequent in the case of engineering schools (the Continental European polytechnics) and in some selected disciplines in particular countries (chemistry in Germany). In the 1960-70s, however, with the development of mass academic education, the scientific revolutions linked mainly to microelectronics and molecular biology (developed mainly in the USA) and the crisis of the traditional industries mainly connected with the polytechnics, in many cases industry-university interaction has further weakened. To remedy this gap, a re-proposition of the “specialized model” has tended to spread in more recent years for the management of the interactions between research and industry and technology transfer. Differently from the US case, where universities have gradually extended their functions (an integrated model centered on universities), one observes in Continental Europe the development of various types of specialized institutions for technology transfer, who act as intermediaries between research and industry (an institutional specialization model).

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<sup>13</sup> An extremely efficient intermediate level of teaching applied disciplines like engineering has been developed (the “Fachhochschulen”), which integrates teaching and practice, but largely overlooks (PTO)

The coupling between scientific, organizational and entrepreneurial capabilities thus constitutes an essential pre-condition for subsequent developments in industry-university relations. However, it is also important to notice that such developments are to some extent to be considered as part of a much more general tendency towards the diffusion of an increasingly favorable attitude towards the establishment and enforcement of strong intellectual property rights.

The establishment of clearly defined property rights played indeed an important role in making possible the explosion of new firm foundings in the US, since the new firms, by definition, had few complementary assets that would have enabled them to appropriate returns from the new science in the absence of strong patent rights (Teece, 1986). In the early years of "biotechnology" considerable confusion surrounded the conditions under which patents could be obtained. In the first place, research in genetic engineering was on the borderline between basic and applied science. Much of it was conducted in universities or otherwise publicly funded, and the degree to which it was appropriate to patent the results of such research became almost immediately the subject of bitter debate. Millstein and Kohler's groundbreaking discovery - hybridoma technology - was never patented, while Stanford University filed a patent for Boyer and Cohen's process in 1974. Boyer and Cohen renounced their own rights to the patent but nevertheless they were strongly criticized for having being instrumental in patenting what was considered to be a basic technology. Similarly a growing tension emerged between publishing research results versus patenting them. Whilst the norms of the scientific community and the search for professional recognition had long stressed rapid publication, patent laws prohibited the granting of a patent to an already published discovery (Merton, 1973; Kenney, 1986). In the second place the law surrounding the possibility of patenting life-forms and procedures relating to the modification of life-forms was not defined. This issue involved a variety of problems (see OTAF, 1984), but it essentially boiled down first to the question of whether living things could be patented at all and second to the scope of the claims that could be granted to such a patent (Merges and Nelson, 1994; Mazzoleni and Nelson, 1995). In fact, these trends were partly spurred by a growing concern about how to exploit more efficiently academic research and by the need to put some order in the system that governed the conditions at

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fundamental research.

which universities could obtain patents – and therefore income - on the results of publicly funded research. The Bayh-Dole Act in 1980 sanctioned these attitudes, by greatly facilitating university patenting and licensing. But as Mowery et al. (1999) have shown, the emergence of the “industry-university complex” (Kenney, 1986) and of the entrepreneurial university pre-dates Bayh-Dole and depends critically on the rise of the two main technological revolutions of the second half of the century, micro-electronics and, especially, biotechnology.

Parallel to Bayh-Dole, a series of judicial and Congress decisions further strengthened the appropriability regime of the emerging sectoral system. In 1980, the US Supreme Court ruled in favor of granting patent protection to living things (*Diamond v. Chakrabarty*), by granting a patent to a scientist working for General Electric who had induced genetic modifications on a *Pseudomonas* bacterium that enhanced its ability to break down oil, and in the same year the second reformulation of the Cohen and Boyer patent for the rDNA process was approved. In the subsequent years, a number of patents were granted establishing the right for very broad claims (Merges and Nelson, 1994). Finally, a one year grace period was introduced for filing a patent after the publication of the invention.

These developments led to an increasing relevance of courts’ decisions upon the fate of individual firms and of the industry in general. Litigation appears to be a distinct feature of the new biotechnology sectoral system and IPR experts have become crucial components of firms’ human resources and competencies. Thus, an increasingly strong property rights regime supported and strengthened the tendencies towards the blurring of the conventional distinction between public and private research. Not only universities, but also institutions like the NIH became increasingly involved in patenting the results of publicly funded research.

In contrast, links between the academy and industry – particularly the ability to freely exchange personnel – have been weaker in Europe. Indeed, the efforts of several European governments were targeted to the strengthening of industry-University collaboration. Thus, one observes a mushrooming of initiatives all across Europe aiming at establishing stronger links between industry and universities and to encourage a more entrepreneurial attitude by universities, rather than the mobility of personnel or the ease for university researchers to establish or participate in companies.

At the same time, policies have been targeted mainly to the set-up of specific organizational devices to manage technology transfer, like science and technology parks or other agencies for technology transfer. These initiatives have taken a wide variety of forms and show a mixed record in their performance and it has been only in very recent times that symptoms of the diffusion of a different attitude have emerged. In some cases, the presence of intermediary institutions has paradoxically increased the distance between University and industry, introducing an additional layer in the relationship instead of creating flexible mechanisms that are not burdened by all sorts of bureaucratic structures and requirements.

On the other hand, in Europe legislation on IPRs took a much less aggressive stance as compared to the USA. In general, the scope for broad claims on patents is greatly reduced and usually process rather than product patents are granted. A draft directive from the Commission that strengthens the protection offered to biotechnology was recently approved by the European Parliament. Still, considerable controversy surrounds this issue.

It is indeed worth stressing that too strong an appropriability regime may not be unambiguously beneficial, especially as it concerns publicly funded research. Increasingly, in the USA doubts are voiced by economists, lawyers and industry analysts that the diffusion of an excessively permissive attitude towards the granting of broad claims on patents might actually slow down the process of diffusion and circulation of knowledge and hence the future rate of technological advance. However, it is also important to notice that the rationale for stronger protection to intellectual property in biomedical research is not based on the traditional argument that the concession of broad property rights is an incentive to the production of knowledge. Rather, the argument is based on the assumption that property rights would favor the creation of markets for technology and hence a faster and more ordered diffusion and use of knowledge (Merges and Nelson, 1994, Mazzoleni and Nelson, 1998).

This argument is however controversial and complex, and cannot be simply accepted at face value in general. Moreover, as several observers have noticed (e.g. David and Dasgupta, 1994, Merges and Nelson, 1994) have argued, this system can seriously undermine the norms and rules of “open science”.

Along with these changes in the intellectual property rights regime and – more generally with the processes of commercialization of science – other long-standing traditional characteristics of the organization and funding of research – which were discussed in Section 4.4 – interacted to produce quite a different environment for the “new” pharmaceutical industry.

As a result of the scientific revolution on the one hand and of the legislation on property rights, the American industry spontaneously developed as an interdependent, integrated and self-sustaining system, characterized by intense flows of people and knowledge between :

- i) the public and private research system : the NIH, other funders and charities; universities and other research institutes ; NBFs and big pharma corporations
- ii) the financial system : venture capital and the Stock Exchange
- iii) the legal system : the Patent Office, the Courts, the patent attorneys within firms.

A few features of this system are worth emphasizing because they are important to understand the similarities and differences between European and American pharmaceuticals.

First, the system did not develop following a deliberated design, but to a large extent it self-organized starting from pre-existing institutions and organizations, adaptively modifying them and creating new ones.

Second, this system is highly decentralized, but also strongly integrated in at least two senses. In one sense, some institutions perform a critical role in orientating and integrating different strands of research and different agents. The NIH represents perhaps the clearest example, as integrator of different lines of basic biological investigation with goal oriented therapeutic research. (Owen-Smith, Pammolli and Riccaboni, 2000). The FDA is another relevant example. In another sense, the system is integrated because different realms and institutions are closely intertwined, are linked by a variety of ties and often perform overlapping functions. Thus, NBFs could not prosper or even exist without the public funding provided to academic research and without the contracts and the qualified demand coming from the large corporations.

Third, the system is self-sustaining, in the sense that each agent perform a complementary function which allows other agents to exist and to act. In other words, there is a high degree of “matching” (Freeman and Perez ; Boyer ; Aoki) between the

various components of the system. However, the system is hardly interpretable as a “Nash equilibrium”, since it is not completely coherent and above all is never in a state of rest. On the contrary, the system is fraught with tensions and conflicts which continuously trigger change. Thus, for example, the decision of the NIH not to allow the patentability of sequences of complementary DNA (c-DNA) induce scientists to start their own company selling these databases for profit. As a consequence, a large pharma corporations decides to put its own database in the public domain, on the grounds (besides other less uninterested motivations) that such knowledge is a research tool and not a product and therefore it should be freely shared and used by the whole research community. But the “NIH spin-off” strikes an agreement with a producer of medical equipment and engages in the ambitious project to decodify the whole humane genome on the basis of the techniques originally developed to construct the c-DNA data bases. Under this challenge, the efforts of the Human Genome Project teams are accelerated and a bitter discussion emerges on the priority and the completeness of the results, on how much the private team has been using publicly generated knowledge, etc..<sup>14</sup>

On the other hand, as time goes by, particular understandings, ways of doing things and solving conflicts as well as techniques and discoveries become widely accepted and are routinely used without little (if any) additional deliberation and discussion (Nelson and Sampat, 2000). Formats of the business plans or standard contracts regulating alliances between NBFs and large corporations become “institutionalized” and serve as template for further modification whenever specific unusual circumstances arise.

Fourth, in a somewhat different but related perspective, one might consider that the emerging system of innovation in the USA is based at the same time on processes of deepening division of labor (typically, as it concerns the specialization of the new biotechnology firms in the early stages of the process of drug discovery and of the large corporations in the following phases) but also – and mainly – on processes of “hybridization” of organizational forms and selective principles. The typical example is obviously given by the overlapping roles, functions and activities of universities, new biotechnology firms and large companies. This process may on the one hand lead to the organizational and institutional innovation; but on the other extent, it might provoke not

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<sup>14</sup> This fascinating history is told and discussed by Rebecca Eisenberg (199x)

only the classical “conflicts of interests” discussed previously, but also to a radical reduction in the degree of variety in the system. If universities, NBFs and large pharma corporations end up looking and acting in very much the same way, efficiency gains stemming from division of labor and differentiation of functions might be foregone and – even more important – the scope for further organizational and technological progress might be reduced, to the extent that each agent act following the same logic and the same principles. In the language of network analysis, the strength of weak ties (Granovetter, 1973) might be replaced by the weakness of strong ties.

Conversely, in Continental Europe this process has progressed to a much slower pace. Besides the legislation on IPRs, the basic structure of universities – and more generally of the research systems - has so far remained pretty much the same as it was 25 years ago, with only few and practically minor exceptions, despite several discussions and various attempts to introduce deep reforms of the academic systems<sup>15</sup>. In general terms, deeply ingrained routines and the very nature of the political processes typical of Continental Europe have so far almost “frozen” the research system. As a consequence, Europe is experiencing neither the advantages nor the shortcomings of the American system. Yet, continuing controversy and discussions on these issues signal that the current state of affairs is not certainly definable an equilibrium one, whatever the concept of equilibrium one might want to use.

## **6. Conclusion**

Regulation touches many different aspects of the pharmaceutical industry, for a large variety of reasons, sometimes directly and explicitly, sometimes indirectly and implicitly. In any case, regulation has always been a critical feature of the industry, albeit in strongly differentiated forms, and it has profoundly impacted on industry evolution and performance.

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<sup>15</sup> For example, in Italy a major reform has been recently introduced, but it is mainly focussed on undergraduate rather than on post-graduate studies and it doesn't really have any strong impact on research. Similarly, the career paths and selection mechanisms of professors have in practice remained unchanged. Another very instructive and sophisticated example of the state of the European debate on these issues is provided by the Research 2000 Report produced by the Swedish Parliament and by the discussions that it provoked afterwards.

Regulation faces in this industry tremendously difficult trade-offs as well as technical and practical difficulties. It is certainly very hard to devise ex-ante and in an abstract way an optimal regulation scheme. The best we can do is devising acceptable and robust schemes, capable of adapting to mutating circumstances.

In fact, the evolution of regulatory regimes has interacted all throughout the history of the industry with the changes in the nature of technological regimes and in the social perceptions of what is considered efficient, just and fair. If anything, regulation is constantly changing, running after the evolution of technology and public perception. Moreover, it follows its own specific trajectories, which are difficult to change and depend on past history, on the institutional settings, etc... Specific problems generate regulation (or lack of it) which in turn create new issues and new problems afterwards. Finally, regulation (or lack of it) is rarely completely coherent. Rather, it is the outcome of differentiated and sometimes seemingly unrelated bits and pieces of intervention in various domains, enacted by different agencies for different purposes (e.g. the Departments of Health, the Treasury, the Departments of Industry and Trade, etc...).

In this perspective, regulation is hardly reducible to simply a reaction to market failures. Rather, what is a market failure is itself largely defined by technology, by the political processes, by the prevailing notions of equity, of what public goods are, etc... As we suggested earlier in this paper, especially when focusing on the innovative performance of this industry, it might be more useful to reason in terms of “systems failures”, rather than market failures. And the judgement on the desirability of alternative degrees and forms of regulation has to do with their relative degrees of coherence and ability to change and react to new circumstances at least as much as with other, more conventional notions of welfare essentially based on static, equilibrium models.

In this paper, we refrained ourselves from advancing too explicit statements on the desirability of certain types of regulation or lack of them. This would have implied a totally different approach and another enormous set of theoretical and detailed empirical papers. However, this brief recount of the evolution of policy regimes in pharmaceutical suggests some very broad – and largely generic – concluding remarks.

On the whole, there seems to be some strong indications that the health of the pharmaceutical industry, especially as innovation is concerned, has been linked to

strong research capabilities coupled with strong domestic and foreign competition. In this sense, competencies and incentives have co-evolved over time. Stifled competition has made it harder – and even impossible - to engage in costly and difficult processes of accumulation of technological and scientific competencies. Conversely, competition alone has not been able to stimulate innovation, in the absence of sufficient levels of pre-existing competencies<sup>16</sup>.

Moreover, it has to be emphasized that competition may take different forms. Quite obviously, the nature of competition in pharmaceuticals is quite different from the standard static pure competition model. On the other hand, there seems to be no simple and unambiguous relation between any single aspect of regulation (e.g. free vs. controlled prices, different systems of inducing cost consciousness, patent regimes, etc..) and performance. Even more so, as soon as it is recognized that regulation is actually composed of very different and interacting types and domains of intervention. Thus, again, it is perhaps more useful to think in terms of “systems of regulation” rather than to isolated policies.

Similarly, there are strong indications that “invasive” command and control oriented approaches are likely to generate distortions, hostility between regulators and companies, resistance to change and are practically difficult to implement efficiently. On the other hand, again, pure market based solutions may simply be unfeasible, let alone desirable, lacking some fundamental preconditions concerning the actual and precise way in which markets work, absent some specific institutions that make it possible for markets to work (e.g. research systems and health care systems) and that take care of the possible negative effects that markets can produce in terms of justice and equity.

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<sup>16</sup> To some extent, this argument might be reduced to the standard notion that the State should be responsible for funding fundamental research and competition in the private sector should stimulate innovative activities. Note, however, that the basis for this notion is usually framed in terms of a public good/ appropriability issue. This is certainly a fundamental aspect of the problem, but not the only one. In a different perspective, the question is that incentives exert their impact only if (some minimum level of) capabilities actually exist. More generally, specific incentives may have very different effects according to the current state and nature of competencies and the processes of accumulation of the latter are not simply plastic to incentives, but follow partly their own autonomous logic, not only as the private-public divide is concerned but also within firms.

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