

Pharmaceuticals as a Sectoral Innovation System

Maureen McKelvey* and Luigi Orsenigo**

*Chalmers University

* University of Brescia and CESPRI, Bocconi University, Milan

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1. Introduction

Pharmaceuticals are a large, high-growth, globalized, and innovation intensive industry. Its products – drugs - 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 and democracy in the new century.

Ever since the last century, pharmaceuticals used to be a traditional stronghold of the European industry and it still provides by far the largest contribution to the European trade balance in high-technology sectors. However, over the past two decades the European pharmaceutical industry has been losing ground vis-à-vis the United States. Moreover, significant changes have also been occurring within European countries (Gambardella, Orsenigo and Pammolli, 2000).

Indeed, over the last two decades, the world pharmaceutical industry has undergone profound transformations. It has been experiencing a series of technological and institutional shocks that have affected all the stages of the value chain and have led to deep changes in firms' organization and in market structure, within domestic markets, regionally, and globally.

At one extreme of the value chain, the advent of what is now known as the “molecular biology revolution” and the emergence of biotechnology have radically transformed the prospects and the processes of drug discovery. At the other extreme, the rise of healthcare costs and prescription drug spending has induced a series of cost containment policies, which have been generating profound changes in the structure of demand in all major national markets. In between, increasingly stringent requirements for the approval of new drugs have implied larger, more costly and internationally based clinical trials. Developments in legislation and in courts' interpretation of issues concerning intellectual property rights, as well as increasing openness of domestic markets to foreign competition are also having significant impacts on patterns of competition and industrial evolution. Jointly, these tendencies have implied a sharp increase in the resources needed to develop new drugs. Equally important, they have led to a redefinition of the nature and of the complementarities between the fundamental sources of competitive advantages in this industry, namely R&D and innovative competencies, marketing and distribution capabilities.

Faced with these challenges, both individual firms and national industries have reacted quite differently. Companies had to redesign their competencies and strategies. In particular, the rising costs and the new logic of R&D and marketing have induced processes of Mergers and Acquisitions (M&A), increasing concentration, and globalization of the industry. At the same time, new patterns of division of labour, collaboration among firms and other institutional actors like universities and

public research centers, are emerging. Key competitive assets for individual firms and countries are increasingly related to knowledge structures as well as the degree of competitiveness and internationalization. These competitive assets include - but are not limited to - the availability of first rate scientific research within universities and other public research centers, the structure of the systems of biomedical research, the patterns of inter-firm alliances in marketing and research.

This chapter analyzes pharmaceuticals and the new biotechnology-pharmaceutical overlap through the lens of a sectoral system of innovation (SSI). Intuitively, the pharmaceutical industry quite naturally lends itself to be analyzed as a Sectoral System of Innovation or as a network (see Galambos and Sewell, 1996; Chandler 1999). However, at the same time and precisely given the intuitive appeal of the notion of “system” and/or “network” for this industry, taking this approach forces the researcher to try to make this notion more precise and compelling and – above all – to “Sectoral Innovation System approach” useful. This constitutes the general aim of this paper. For the time being, we start from the provisional definition proposed by Franco Malerba in his contribution to this project:

A sectoral system of innovation and production is composed by the set of heterogeneous agents carrying out market and non-market interactions for the generation, adoption and use of (new and established) technologies and for the creation, production and use of (new and established) products that pertain to a sector (“sectoral products”).

Generically, the pharmaceutical industry can be easily considered as a system or a network because innovative activities involve directly or indirectly a large variety of actors, including: (different types of) firms, other research organizations like universities and public and private research centers, financial institutions, regulatory authorities, consumers.

All these actors are different in many senses. They know different things, they have different incentives and motivations, they have different rules of action.

All these actors are linked together through a web of different relationships. Starting from a standard economic approach, such relations are quite varied, as they include almost pure market transactions, command and control, competition, collaboration and cooperation and all sorts of the so-called “intermediate forms”. Already at this extremely simplistic level of discussion, the pharmaceutical industry looks quite interesting because some – if not most – of these relationships have a peculiar nature. The obvious example is the observation that the market for drugs is characterized by strong informational asymmetries. Consumers cannot properly evaluate the

quality of a drug; those who select a particular drug for a specific consumer do not coincide with those who pay for the drug, etc.. Another obvious example is given by the relationships between universities and other research institutions on the one hand and industry on the other. These agents act following different logics, incentives and goals, which may often conflict. The interaction is affected by the actions of regulatory authorities, e.g. patent laws, incentives to academics to engage in commercial activities, etc.. In particular, in this industry, one observes the mix and partial overlapping of different selection principles. As we shall argue, the emergence of hybrid forms of selection and learning (Mc Kelvey, 1997) is one of the most interesting features of this industry in recent years.

In this paper, we try to articulate this perspective addressing four issues, which link our empirical analysis of this sector with theoretical arguments. These four issues are:

- First, the relative importance of these actors and the specific form of the linkages between the actors differs over time and across countries.
- Second, this system has been changing over time through the emergence of new agents and of new relations, and through changes in the intensity of these relationships.
- Third, the key capabilities and competitive assets have changed, due to environmental selection pressures as well as to internal firm actions.
- Fourth, this in turn implies that patterns of competition and selection processes have also changed in the international pharmaceutical sectoral system of innovation.

Rather than identify and map each national element within European countries or more internationally within the pharmaceutical sectoral system of innovation, this chapter instead selects a subset of problems and conceptual issues to analyze. The boundaries of our analysis can be set as follows:

- a) First, we do not focus on the entire history of the industry, but only on a recent period. In particular, although we sketch the evolution of the industry prior to the mid Seventies, as a background for the following analysis, we examine mainly the evolution of the pharmaceutical industry over the last 20/25 years. That is to say, we concentrate on the impact of the molecular biology revolution and – to a lesser extent – on the effects of cost-containment policies. The main reason for this choice is that these major changes in supply, demand and knowledge development have profoundly modified the structure of the relationships among firms and the other agents that define this sectoral system of innovation.
- b) Second, we focus on the dynamics of the system. Rather than trying to provide a detailed examination of the structure of the system at a given point in time, we concentrate on trying to make some steps in understanding how the system evolves over time, both in response to

“external shocks” and as a result of endogenous developments in the network itself. This attitude reflects the basic methodological stance that the notion of sectoral systems of innovation has an intrinsic dynamic and evolutionary connotation and that – in order to understand why a specific structure takes a particular form – one has to understand the dynamic processes that generated it. We look at industry evolution as a dynamic disequilibrium and evolutionary processes, a process of imperfect adaptation through the construction and reconfiguration of organizational capabilities.

- c) Third, we focus on the changing nature of the relationships among selected agents, rather than on specific agents. Relationships are obviously at the heart of sectoral system of innovation, with the idea that no firm innovates in isolation but is instead an integral actor within collective market and knowledge processes. For these reasons, we try to reconstruct and to understand how differentiated forms of interaction among agents have changed over time and why.
- d) Fourth, we focus on the interaction between cognitive/technological factors and institutional/country-specific factors that shape the evolution of the pharmaceutical system of innovation. Both factors are clearly relevant, and one contribution here is to analyze how and why both meet and shape pharmaceutical competition. On the one hand, changes in the knowledge base and in the relevant learning processes have induced deep transformations in the behaviour and structure of the agents and in their relationships among each other. On the other hand, the specific way these transformations have occurred across countries has been profoundly different, in relation to the details of the institutional structure of each country. Understanding how technology and institutions co-evolve is a major aim of this paper.

The analytical arguments for including institutions and incentives influencing demand, supply and knowledge development are that these three together form the specific innovation opportunities for pharmaceuticals. Moreover, the specific innovation opportunities for pharmaceuticals are also shaped by the actions of individual firms and of groups of firms. Thus, firms also shape these innovative opportunities through their forward looking decisions, strategies, actions as well as past competencies. Nevertheless, we argue that on the one hand, it is reasonable to group firms relative to their reactions to specific national selection environments, while on the other hand, firms will not react identically to such environments, leading to some diversity within a group of firms.

Thus, we compare the evolution of the sectoral systems of innovation in pharmaceuticals in the USA and in Europe. In particular, the Continental European pharmaceutical sectoral systems of innovation differs in significant ways from the Anglo-Saxon ones. The focus here will be on the larger Central European countries of Germany, France, Italy compared to US and UK. These

historically rooted differences are visible and impact firms in significant ways, despite strong international links and international trends.

Our view of the pharmaceutical sectoral system of innovation combines analytical perspectives based on theory with rich empirical material. We do not present here directly new empirical evidence and data. Rather, we rely on secondary sources (some of it provided by the authors), to which readers are referred .

Specifically, the paper is organized as follows. In Section 2, we briefly recount the main features of the development of the pharmaceutical industry until (more or less) the Mid-Seventies. We discuss in particular the interactions between the nature of the learning regimes and the related forms of organization of innovative activities; the patterns of competition and the nature of firms' and countries competitive advantages; the forms of regulation and the structure of demand.

In Section 3, we move to the more recent history. Here, we discuss how the changes in the knowledge base and in the technological regime induced by the advent of the Molecular Biology Revolution on the one hand and by the transformations in the regulatory environment and in demand on the other have drastically reconfigured the sectoral system of innovation. First, we look at the American case. Then, against this background, we discuss the main factors that might have caused a decline in European competitiveness.

On these grounds, Section 4 tries to link historical evidence with more theoretically oriented analysis. In this final section of the paper, some conclusions and hypotheses are suggested which relate to the general concept of a sectoral system of innovation and are applied both to the specifics of pharmaceuticals and the specifics of Europe.

2. Innovation and the evolution of the sectoral system of innovation in the pharmaceutical industry: an overview

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 section 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 above all Henderson, Orsenigo and Pisano, 1999. These references have, however, been used to give an interpretation of the history of the pharmaceutical industry in terms of our evolutionary approach to systems of innovation (McKelvey 1997).

In very general terms, the history of the pharmaceutical industry can be analyzed as an evolutionary process of adaptation to major technological and institutional “shocks”. These shocks have occurred both endogenously and exogenously to the sector, and they include our three dimensions of supply, demand and knowledge development. While radical changes seem to characterize change within this sector, past interrelated shocks can be useful to divided modern history 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.

2.1 The early stages of the pharmaceutical industry

The first epoch corresponds roughly to the period 1850-1945. This is the period where drugs were closely related to chemicals, especially with the emergence of the synthetic dye industry in Germany and Switzerland. In terms of novelty generated, this epoch was one in which little new drug development occurred, and in which 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.

Nevertheless, firms in other geographic localities were also moving into pharmaceuticals. In the U.S. and the U.K., mass production of pharmaceuticals also began in the later part of the 19th century. However, whereas Swiss and German pharmaceutical activities tended to emerge within larger chemical producing enterprises, the U.S. and U.K. witnessed the birth of specialized pharmaceutical producers such as Wyeth (later American Home Products) Eli Lilly, Pfizer, Warner-Lambert, and Burroughs-Wellcome. As organizational forms, these were more specialized and independent drug producers, rather than an integral part of chemical companies.

Overall in these early years, the pharmaceutical industry was not tightly linked to formal science nor 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. Most new drugs were based on existing organic chemicals or were derived from natural sources (e.g. herbs) and little formal testing was done to ensure either safety or efficacy. However, the emerging sectoral system of innovation comprised already not only firms, but quite obviously also universities and – to a lesser extent, since regulation was not strongly developed - regulatory authorities. Universities provided the basic knowledge in chemistry and – most importantly – the

inflow of trained chemists necessary to sustain innovation. Similarly, patent laws (where available) provided both the incentives and the context for innovation.

Moreover, linkages among firms quickly developed due to the exchanges of licences for production and marketing of drugs. These licensing relationships are important for the industrial structure of the sector, because they helped create differentiated categories of pharmaceutical firms. Indeed, ever since its inception, the industry has been comprised of – at least – two types of firms. A first group of companies focused relatively more on innovation and drug discovery, and this group included the German and Swiss giants and some American companies like Merck, Pfizer (see Chandler, 1998). These companies have been focused on first mover advantages through drug discovery and commercial exploitation. A second group of firms has instead specialized in being followers in the sense of imitating / inventing around products invented elsewhere and/or products sold over-the-counter. This group of firms included companies like Bristol-Myers, Warner-Lambert, Plough, American Home Products as well as most of the firms in countries like France, Italy, Spain and Japan. Both groups of companies have developed their own types of production and marketing competencies, but the main differences seem to be in overall strategies for innovations.

2.2 The “Random Screening” period

The second epoch runs approximately from 1945 to the early 1980s, where the golden age of pharmaceuticals began in earnest after World War II. 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 gradually to set the stage for its subsequent dominance. We suggest some possible explanations for these trends in the following paragraphs.

2.2.1 The organization of R&D and the patterns of competition

This second epoch 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 during this second epoch. 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 cardiovascular and central nervous system products -- pharmaceutical companies faced an almost completely open field. Remember that before the discovery of penicillin, very few drugs effectively cured diseases. This situation can be called a target rich environment, in the sense that many possible targets were available - with attenuate high probabilities of success.

Faced with such a "target rich" environment but with very little detailed knowledge of the biological underpinnings of specific diseases, pharmaceutical companies invented an approach to research now referred to as "random screening." Under this approach, natural and chemically derived compounds are randomly screened in test tube experiments and laboratory animals for potential therapeutic activity. Pharmaceutical companies maintained enormous "libraries" of chemical compounds, and they added to their collections by searching for new compounds in places such as swamps, streams, and soil samples. Thousands of compounds might be subjected to multiple screens before researchers honed in on a promising substance. Serendipity played a key

role since in general the "mechanism of action" of most drugs were not well understood. Researchers generally relied on the use of animal models as screens.

Under this regime it was not uncommon for companies to discover a drug to treat one disease while searching for a treatment for another. Still, search was directed by the limitations of search itself. Since even the most productive chemist might find it difficult to synthesize more than a few compounds over the course of a week, researchers tended to focus their attention on synthesizing variants of compounds that had already shown promising effects in a screen, but that might not be ideally suited to be a drug. Important limiting factors in this target rich environment were that any given compound might have unacceptable side effects or be very difficult to administer. While chemists working within this regime often had some intuitive sense of the links between any given chemical structure and its therapeutic effect, little of this knowledge was codified, so that new compound "design" was driven as much by the skills of individual chemists as it was by a basis of systematic science.

The "design" of new compounds was a slow, painstaking process that drew heavily on skills in analytic and medicinal chemistry. Several important classes of drugs were discovered in this way, including most of the important diuretics, many of the most widely used psychoactive drugs and several powerful antibiotics. This nature of the processes of drug discovery and development had an important impact on the patterns of competition and on market structure in that innovative R&D intensive companies were profitable and competitive. Competition and market structure are in turn dependent on the strategies and fortunes of individual companies, which are sometimes linked to different national contexts and sometimes part of international trends.

Indeed, random screening worked extremely well for many years. Several hundred new chemical entities (NCEs) were introduced in the 1950s and 1960s, and several important classes of drug were discovered in this way. The outcome in terms of medicine was thus significant and increased the supply and diversity of drugs available to treat diseases. Nevertheless, the search process itself was rather inefficient, and so the successful introduction of NCEs has to be considered as a quite rare event. Estimates suggest that, out of all new compounds that were tested only one out of 5,000 reached the market. The rate of introduction was on the order of a couple of dozens per year, and these were concentrated in some fast-growing areas such as central nervous system, cardiac therapy, anti-infectives and cytostatics. In short, innovative new drugs arrived quite rarely but after the arrival they experienced extremely high rates of market growth. In turn, this entailed a highly skewed distribution of the returns on innovation and of product market sizes as well as of the intra-firm distribution of sales across products. So a few 'blockbusters' dominated the product range

of all major firms (Matraves, 1999, p.180; Sutton, 1998). The firms were dependent on these singularly successful products, which also had rapidly growing markets.

The success of this way of organization of the innovation process led to a favoring of certain types of innovations (McKelvey forthcoming), which was reinforced by mechanisms of appropriability of the potential profits deriving from innovation. 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.

Note, however, that the scope and efficacy of patent protection has varied significantly across countries. The U.S have provided relatively strong patent protection in pharmaceuticals. However, in 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. France introduced product patents in 1960, Germany 1968, Japan 1976, Switzerland 1977, Italy and Sweden in 1978. In some 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 other cases, primarily Germany and Switzerland, this negative effect didn't happen. 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.

In addition to external national institutions, however, factors internal to specific firms also clearly affected the survival of certain firms - in terms both of their ability to continue - and success at - competing over time. Such factors also affect the ability for firms outside the industry to enter. 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 itself. 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 access to the appropriate information infrastructure for their therapeutic areas.

However, entirely new products (New Chemical Entities) only capture a part of innovative activities, even in this second epoch. Other ways of innovating and appropriating economic returns were also important, both to a second group of firms as well as to leading innovating firms. "Inventing-around" existing molecules, or introducing new combinations among them, or new ways of delivering them, etc., constituted a major component of firms' innovative activities broadly defined. Thus, while competition centered around new product introductions, firms also had to compete through incremental advances over time, as well as imitation and generic competition after patent expiration. This latter in particular allowed a large "fringe" of firms to thrive through commodity production rather than radical innovation. Generations of new markets and of diversification across product groups was followed by processes of incremental innovation, development of therapeutic analogues, imitation, licencing. One reason that both the first-comer innovators and other early innovators could steadily grow in this second epoch was the quickly expanding markets, for specific drugs and for pharmaceuticals as a whole.

Again, internal to the firm factors could give competitive advantage because the firm could organize and control a series of related assets necessary for economic appropriation of innovation - or of imitation. This is because the successful exploitation of the economic benefits stemming from innovation also required control over other important complementary assets. These included, in particular, competencies in the management of large-scale clinical trials, in the process of gaining

regulatory approval, in marketing and distribution. Taken together with strong incentives to be first innovator with solid patents, these factors also acted as powerful barriers against entry into the industry.

As a consequence of these selection pressures on individual firm choices, the international pharmaceutical industry has been characterized by a significant heterogeneity in terms of firms' strategic orientations and innovative capabilities. The "innovative core" of the industry has been composed by the early German innovative entrants, which were joined after World War II by a few American and British firms. These maintained an innovation-oriented strategy over time with both radical product innovations and incremental product and process innovations. A second group of firms - either located in these countries or more likely in other countries like continental Europe and Japan - specialized instead in imitation, minor innovations and marketing.

Likely due to the above pressures, the international industrial structure was rather stable up to the mid-1970s, with very few entrants. The reasons explaining this are the mechanisms providing the appropriability of innovations, combined with the presence of scale economies in pharmaceutical research, and marketing. Indeed, many of the leading firms during this period -- companies like Roche, Ciba, Hoechst, Merck, Pfizer, and Lilly -- had their origins in the "pre-R&D" era of the industry. At the same time, until the mid-1970s only a small number of new firms entered the industry, and even fewer could enter the "core" of successful innovative firms. Despite this stability in industrial structure, pharmaceuticals has been a series of fragmented markets. The industry was characterized by quite low levels of concentration, both at the aggregate level (the pharmaceutical industry) but also in the individual sub-markets like e.g. cardiovascular, diuretics, tranquilizers, etc.

Finally, in this period the pharmaceutical industry started to become truly international. The high weight of sunk costs in R&D and marketing implied expansion into new markets to reduce average costs. Moreover, the presence in foreign markets was often necessary for complying with local regulation. Not particularly surprising, it was the largest, highly R&D intensive German, Swiss and American companies that proceeded more decisively in their international expansion, establishing also networks of relations with local firms through licensing and commercialization agreements.

2.3 Changes in the network of relations

In this second epoch, the network of relations defining the pharmaceutical sectoral system of innovation underwent deep transformations. Still, rather than a drastic change in the structure of the network, relationships among agents became denser and thicker.

A continuing analysis of this second epoch based on our four original issues brings us back to the issues of co-evolution of supply, demand and knowledge development. Two points are particularly important to consider during this second epoch, mainly because they lay the foundation for understanding the transformation into the third epoch, from the early 1980s. These two points relate to the co-evolution of market, institutions and knowledge. The first point is that new challenges and opportunities arose, not least due to investments in basic medical science, major changes in drug regulation, and the increases in final demand due to collectivized health care. The second point is that the differing positions of countries in respect to these three factors apparently led to different reactions among their constituent populations of firms. The evidence presented here mainly compares and contrast continental European countries with the Anglo-Saxon experience, although some evidence about the small, open economies with high knowledge investment are also presented in order to return to their different paths of development in the conclusions.

2.3.1 Biomedical research: funding and organization

A first change during the second epoch which would fundamentally affect the transformation to the third epoch concerns fundamental research and industry-university relations. 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). Many good European scientists relocated, of course, to the USA due to the wartime situation. In the specific case of biomedical research, in this period, linkages with universities and basic research consolidated and started to change their nature, as a consequence of the increase in public spending for biomedical research and due 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 and in the ways in which it is spent. 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 allows 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 done 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 is administered through the NIH, although a significant fraction goes to universities and an important fraction of the support does go towards basic or fundamental science that is widely disseminated through publication in the refereed literature. Still, the orientation towards health is implicit when not explicit. Moreover, the American system has been characterized by a variety of sources of funding and selection mechanisms, which complement the role of the NIH and act - always starting from scientific excellence - according to different allocative principles. This approach introduces some form of competition between financiers, and so it allows diversity to be explored, while also maintaining this emphasis on quality, fundamental science. This enables 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 centres of excellence. 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 constitute 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 favouring 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 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 is 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. During the third epoch, private foundations such as the Wellcome Trust have also emerged as major sources of funding. The MRC funds 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 is 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 are the DFG (Deutsche Forschungsgemeinschaft) and the MPG (Max Planck Gesellschaft). DFG funds external research, while MPG receives 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 produces less science of generally lower quality but also one in which science is 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 result 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 that 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).

2.3.2 Procedures for product approval

A second fundamental change during this second epoch which has changed the competitive environment has to do with the procedures for product approval. Since the early 1960s, most countries have steadily increased the stringency of their approval processes. However, it was the USA, with the Kefauver-Harris Amendment Act in 1962, and the UK, with the Medicine Act in 1971, that took by far the most stringent stance early on among industrialized countries. Germany but especially France, Japan, and Italy have historically been much less demanding. Other countries fall somewhere in-between.

In the USA, the 1962 Kefauver-Harris Amendments introduced a proof-of-efficacy requirement for approval of new drugs and established regulatory controls over the clinical (human) testing of new drug candidates. 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 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 1) large increases in the resources necessary to obtain approval of a new drug application (NDA), 2) they probably caused sharp increases in both R&D costs 3) and in the gestation times for new chemical entities (NCEs), 4) along with large declines in the annual rate of NCE introduction for the industry as well as 5) 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 favouring 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 firms¹.

The institutional environment surrounding drug approval in the U.K. was quite similar to that in the U.S. 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

¹ Until the Waxman-Hatch Act was passed in the U.S. in 1984, generic versions of drugs that had gone off patent still had to undergo extensive human clinical trials before they could be sold in the U.S. market, so that it might be years before a generic version appeared even once a key patent had expired. In 1980, generics held only 2% of the U.S. drug market.

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.

In Continental European countries, procedures for products approval were far less stringent. 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 firms from the other European countries have fared better than Continental European firms 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).

The development of increasingly demanding and sophisticated clinical trials necessary for the approval of drugs had a further effect on the pattern of industry-university relations, strengthening the interaction between companies and hospitals linked to medical schools in the design and implementation of increasingly scientifically-based trials. In effects, the main channel of interaction between pharmaceutical companies and universities continued to be 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”.

2.3.3 Demand Growth, the Development of Health Care Systems and Regulation

A final 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 were 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. In the U.S., 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 blockbusters.

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

The main reason for price regulation was 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 efficiency – argument referred (albeit not always explicitly) to some peculiar features of the market for drugs. First, demand elasticity tends to be low, given the value that users may attribute to the product, especially in extreme cases. Second, the market for drugs is inherently characterized by information asymmetry. Producers have “more information” on the quality of the drug than consumers. In fact, it is physicians and not patients that take the decision about the use of alternative drugs, but even doctors cannot know in detail the properties of a drug, especially when a drug is new. Moreover, it was observed that much of the information available to physicians is provided by the companies themselves. Producers could then try to exploit this asymmetry by charging higher prices. Finally, it was usually stressed that producers enjoy monopoly power through patent protection. Price regulation might therefore be justified as a mechanism to countervail monopolistic pricing. 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 the Kefauver Committee (see Comanor 1986 for a survey).

A further set of reasons for price regulation referred 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.

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

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

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 Pharmaceutical Price Regulation Scheme, formerly known as Voluntary 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 Services². 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 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

² A similar system has been adopted in the regulation of public utilities under private ownership such as electricity and water supply.

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 favour 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 competitors³) 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 payed and the consumer did.

In both France and Japan, such controls have proven, according to many observers authors, 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.

In sum, in this second epoch, industrial leadership was based on the combination of strong technical and organizational capabilities in the innovative process within innovative firms, competencies (sometimes and in some countries also or even mainly of a “political” nature) in the processes of products approval, marketing and distribution. Moreover, the processes and the intensity of competition, largely shaped by institutional factors like patent legislation, procedures for product approval and price regulation tended to favour in some cases the more innovation-oriented firms, in other cases the marketing-oriented companies, and even the less efficient smaller firms mainly operation 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 favouring the adoption of innovative strategies. Moreover, it worth noting that many of these institutional arrangements were not devised with the explicit aim of favouring innovation or even industrial prowess. Rather, they resulted from totally different purposes - like social policies - but ended up – after sometimes quite prolonged periods of time - bearing important consequences on the capacity and willingness to innovate.

3. The Advent of Molecular Biology and the Age of Cost-Containment

The third epoch in our characterization runs from the early 1980s 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 demand⁴.

Beginning in the early Seventies, the industry also 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

³ 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.

⁴ Although the earliest scientific expressions of molecular biology were visible from the mid-1970s and some pharmaceutical companies were quick to explore this route, we have set the rough period of the third epoch from the early 1980s through the present to take into account of when more major impacts of modern biotechnology were felt within pharmaceuticals.

areas transformed radically the cognitive and organizational nature of the processes of learning and discovery. Moreover, if firms wished to create and sustain learning processes within these new knowledge bases, they had to be part of a new system, with new structure of incentives.

This section concentrates on discussing how and why changes in the knowledge bases and in the related “learning regime” have altered the structure of the sectoral system of innovation, especially when put in relation to the changing nature of demand. Moreover, this section addresses some of the main consequences of such a shift for explaining the relative competitiveness of the population of firms in biotechnology-pharmaceuticals in different countries. The main comparison is again between Continental Europe and Anglo-Saxon countries, with some reference to the small open economies of Europe.

3.1 The Scientific revolution and the new learning regime

From the middle Seventies on, substantial advances in physiology, pharmacology, enzymology and cell biology -- the vast majority stemming from publicly funded research -- led to enormous progress in the ability to understand the mechanism of action of some existing drugs as well as the biochemical and molecular roots of many diseases. This new knowledge and related techniques and equipment had a profound impact on the process of discovery of new drugs within pharmaceutical firms. First, these advances offered researchers a significantly more effective way to screen compounds. In turn the more sensitive screens made it possible to screen a wider range of compounds, triggering a "virtuous cycle" of discovery and understanding. In other words, the availability of drugs whose mechanisms of action was well known made possible significant advances in the medical understanding of the natural history of a number of key diseases. These advances in turn opened up new targets and opportunities for drug therapy. Combining medical understanding with an understanding of disease and drug action enabled the firms to concentrate on areas likely to give further returns. This can be called 'guided search'.

These techniques of "guided search" made use of the knowledge that a particular chemical pathway was fundamental to a particular physiological mechanism. If, to use one common analogy, the action of a drug on a receptor in the body is similar to that of a key fitting into a lock, advances in scientific knowledge in the seventies and eighties greatly increased knowledge of which "locks" might be important, thus making the screening process much more precise. This implies that the firm R&D process itself can become more efficient through search within a more precise and better defined search space (McKelvey 1997). Following the continuous advances in basic science, this process has become more efficient over time and, more recently, it has led to an improved understanding of what suitable "keys" might look like. Chemists are now beginning to be able to

"design" compounds that might have particular therapeutic effects. The techniques of "rational drug design" are the result of applying the new biological knowledge to the design of new compounds, as well as applying it to the ways in which the compounds are screened.

Knowledge advances, however, had no automatic effect on the strategies and competitiveness of any given firm. Or, to put it the other way, these techniques were not uniformly adopted across the industry. For any particular firm, the shift in the technology of drug research from "random screening" to one of "guided" discovery or "drug discovery by design" was critically dependent on the ability to take advantage of publicly generated knowledge (Gambardella, 1995; Cockburn and Henderson, 1996) and of economies of scope within the firm (Henderson and Cockburn, 1996). Smaller firms, those farther from the centers of public research and those that were most successful with the older techniques of drug discovery appear to have been much slower to adopt the new techniques than their rivals (Gambardella, 1995; Henderson and Cockburn, 1994;). There was also significant geographical variation in adoption. While the larger firms in the US, the UK and Switzerland were amongst the pioneers of the new technology, other Continental European and Japanese firms appear to have been slow responding to the opportunities afforded by the new science. In Scandinavia, however, some firms were in quite quickly. These differences in the initial changes within drug development techniques seems to have significant implications for the later response of the population of pharmaceutical firms to the revolution in molecular biology.

This transition towards new techniques of drug discovery was in mid-course when molecular genetics and rDNA technology opened an entirely new frontier for pharmaceutical innovation. The application of these advances initially followed two relatively distinct technical trajectories. One trajectory was rooted in the use of genetic engineering as a process technology to manufacture proteins whose existing therapeutic qualities were already quite well understood in large enough quantities to permit their development as therapeutic agents (McKelvey 1996). The second trajectory used advances in genetics and molecular biology as tools to enhance the productivity of the discovery of conventional "small molecule" synthetic chemical drugs. More recently, as the industry has gained experience with the new technologies, these two trajectories have converged.

More recently, technologies such as genomics, gene sequencing, transgenic animals, and molecular biology have started to supply the industry with a huge number of novel biological targets thought to be relevant to a vast array of diseases defined at the molecular level, and to develop highly sensitive assays incorporating these targets. Against this background, during the Eighties and Nineties new developments in a variety of research areas has affected both the search and testing phases of pharmaceutical research and development. These advances include a variety

of things, such as solution phase and solid phase chemistries, high-throughput screening technologies (HTS), information technologies, and combinatorial chemistry. These have led to the development of a set of research technologies that allow to achieve a higher breadth of applications, measured in terms of the number of disease areas and biological targets to which the firm may apply these technology.

One of the important consequences of these parallel improvements in knowledge, techniques and equipment in a variety of fields is that a larger number of targets can be tested, even if each one is thought to be more likely to be relevant for something. For example, the methods of conventional medicinal chemistry could not allow the company to test several thousand genetic targets, but the development of combinatorial chemistry libraries, together with new techniques for high-throughput screening and ever-improving bio-informatics tools, has gradually made it possible to test a large number of potential drug targets against an even larger number of chemical entities⁵ This move towards large numbers has been accompanied by knowledge development which also increases the speed at which each is tested. Thus, more generally, during the Nineties, a set of generic research technologies has been developed (from PCR, to protein structure modeling, rapid computer based drug assay and testing, recombinant chemistry techniques, drug delivery systems, chemical separation and purification techniques) that allow researchers to screen thousands of potentially promising compounds at an unprecedented speed.

The appearance of these new family of technologies has introduced a further distinction in the (co-existing) search regimes characterizing contemporary pharmaceutical R&D. The first regime is essentially based on biological hypotheses and molecules that tend to be specific to given fields of application (co-specialized technologies) while the second regime is characterized by the emergence of new generic tools useful in searches based on the law of large numbers (labeled in the literature as transversal or generic or platform technologies).

In the case of co-specialized research hypotheses and molecules, the characterization of biological targets and the corresponding design/experimentation of each new drug tends to require individual analysis. Lessons learned from the design and experimentation of one biological hypothesis/molecule cannot be immediately transferred to other biological domains, in order to develop other classes of drugs. Conversely, transversal technologies are in principle applicable to

⁵ Combinatorial chemistry enables rapid and systematic assembling of a variety of molecular entities, or building blocks, in many different combinations to create tens of thousands of diverse compounds that can be tested in drug discovery screening assays to identify potential lead compounds. Large libraries are available to be tested against both established and novel targets to yield potential lead compounds for new medicines. Such vast numbers of compounds have been introducing a substantial challenge to the drug discovery process and have created a need for faster and more efficient screening. High-throughput screening (HTS) methods make it possible to screen vast populations of compounds via automated instrumentation: that is, complex workstations capable of performing several functions with the help of mechanical arms or simpler automated dilution devices.

multiple biological targets and diseases. The search space is possible across many applications, but have to made specific for each use (Orsenigo, Pammolli and Riccaboni, 2001).

These changes in the knowledge bases have been here been described as particularly relevant to pharmaceutical firms in the drug discovery and development phases. These shifts were, moreover, partly exogenous to the pharmaceutical sector in the sense that fundamental research and access to relevant materials, techniques and equipment might come outside the search activities of the firms themselves. At the same time, these shifts have been endogenous in that their adaptation - and further modification to be relevant to the concerns of business - have occurred within firms. Taken together, this section has described them as a new learning regime, which the next section argues is relevant for determining the industrial structure as well as the division of knowledge labor within the international pharmaceutical sectoral system of innovation.

3.2 From learning regime to organization of innovative activities within and across firms

In this third epoch, the advent of modern “biotechnology” has had a significant impact on both the organizational competencies required to be a successful player in the pharmaceutical industry and on industry structure in general. The co-evolution of knowledge, institutions and organizational forms of research within the pharmaceutical sectoral system of innovation has also influenced the relative success and failure of specific firms trying to adapt and influence the new learning regime.

As compared to the “random screening regime” of the second epoch, the new learning regime found in our third epoch has required different learning and discovery procedures. Basically, the new knowledge bases have influenced the organizational structure of innovative activities, both as distributed within firms as well as distributed across different firms and non-firm organizations within this sectoral system. The reason the organizational structure has changed in such significant ways is that new knowledge bases have led to a new structure of the search space, new definitions of the problems to be solved, other heuristics and routines used to solve such problems. For reasons argued below, these changes in turn have lead to a redesign of the patterns of division of labour, to different incentive structures and selection mechanisms.

The process of transition to the new paradigm marks the shift which defines this third epoch. This transformation occurred much more quickly in the USA than in particularly Continental Europe, while also taking profoundly different forms. In understanding these shifts, it is important to break the discussion into new biotechnology firms as compared to established pharmaceutical firms, mainly in order to later identify their respective, specialized roles within the sectoral system

of innovation. Moreover, we shall deal first with the American case and then we suggest some hypotheses as to why Europe lagged behind.

3.2.1 New Biotechnology Firms

The most noticeable manifestation of the transformations occurring in the pharmaceutical SSI has been the appearance of a new breed of agents, i.e. new specialized biotechnology firms (NBFs). As in many other technologies, innovation was firstly pursued not by incumbents but by new companies. In the United States, biotechnology was the motive force behind the first large scale entry into the pharmaceutical industry since the early post World War II period. The first new biotechnology start-up, Genentech, was founded in 1976 by Herbert Boyer (one of the scientists who developed the recombinant DNA technique) and Robert Swanson, a venture capitalist. Genentech constituted the model for most of the new firms. They were primarily university spin-offs and they were usually formed through collaboration between scientists and professional managers, backed by venture capital. Their specific skills resided in the knowledge of the new techniques and in the research capabilities in that area. The “function” of this type of NBF has been to mobilize fundamental knowledge created in universities and to transform it into potentially commercially useful techniques and products. Their aim consisted in applying the new scientific discoveries to commercial drug development, focussing on two main directions: diagnostics, on the basis of monoclonal antibodies, and therapeutics.

It is indeed interesting to ask why the transfer of fundamental, academic knowledge to industry involved the creation of new organizational entities like the NBFs rather than some sort of direct relationship between large pharmaceutical firms and universities. At this stage, let us just remark that the internal organizational structure of the NBFs reflected their origin and competencies. They were organized very much like academic units and they deeply embodied some fundamental academic principles like the importance attributed to publication and to work at the frontier of knowledge. However, these organizational principles (in terms of norms, incentives, practices) had to be made consistent with their commercial nature too. Thus, secrecy and the search for broad property rights became crucial features of these new firms. Moreover, financial constraints coupled with their high burn rates have made “time to patent” a characteristic feature of the research style of these companies.

Genentech was quickly followed by a large number of new entrants. Entry rates soared in 1980 and remained at a very high level thereafter, but with waves linked to both the stock market performance and to the appearance of successive new technologies. Despite the high rates of entry of new firms into biotechnology, it took several years before the biotechnology industry started to have an impact on the pharmaceutical market. Many of the early trajectories of research proved to

be dead-ends and/or much more difficult to develop than expected, as for example in the case of interferon⁶. Note, however, that while NBFs have transformed pharmaceutical industry world-wide, much of the motor of change within modern biotechnology has occurred in the USA. More NBFs have been started in the USA, and they tend to have agreements with pharmaceutical firms around the globe.

While biotechnology related products became integrated with pharmaceuticals, the large majority of these new companies never managed to become a fully integrated drug producer. The growth of NBFs as pharmaceutical companies was constrained by the need to develop competencies in different crucial areas, including both scale and scope of knowledge bases as well as complementary assets.

First, as far as the first generation of NBFs is concerned, they found it necessary to understand better the biological processes involved by proteins and to identify the specific therapeutic effects of such proteins. Companies, in fact, turned immediately to produce those proteins (e.g. insulin and the growth hormones) which were sufficiently well known. The subsequent progress of individual firms and of the industry as a whole was however predicated on the hope of being able to develop much deeper knowledge of the working of other proteins in relation to specific diseases. Yet, progress along this line proved more difficult - and more expensive - than expected.

Second, these companies often lacked competencies in other different crucial aspects of the innovative process: in particular, knowledge and experience of clinical testing and other procedures related to product approval on the one hand and marketing on the other. Some like Genentech worked to hire a range of persons with appropriate skills while others remained more specialized in their activities. Thus, many of these NBFs have exploited their basic competence and acted primarily as research companies and specialized suppliers of high technology intermediate products, performing contract research for and in collaboration with established pharmaceutical corporations.

Third, even remaining at the level of pre-clinical R&D, most NBFs lacked crucial competencies in a rather different way. In fact, many individual NBFs were actually started on the basis of a specific hypothesis or technique, following the processes of growth of knowledge in the

⁶ The first biotechnology product, human insulin, was approved in 1982, and between 1982 and 1992, 16 biotechnology drugs were approved for the US market. As is the case for small molecular weight drugs, the distribution of sales of biotechnology products is highly skewed. Three products were major commercial successes: insulin (Genentech and Eli Lilly), tPA (Genentech in 1987) and erythropoietin (Amgen and Ortho in 1989). By 1991 there were over 100 biotechnology drugs in clinical development and 21 biotechnology drugs with submitted applications to the FDA (Pharmaceutical Manufacturers Association, 1991, Grabowski and Vernon, 1994): this was roughly one third of all drugs in clinical trials (Bienz-Tadmor et al., 1992). Sales of biotechnology-derived therapeutic drugs and vaccines had reached \$2 billion, and two new biotechnology firms, (Genentech and Amgen) have entered the club of the top eight major pharmaceutical innovators (Grabowski and Vernon, 1994).

field. Such processes entailed the proliferation and branching of alternative hypotheses at increasing levels of specificity (Orsenigo, Pammolli and Riccaboni, 2001). Thus, successive generations of NBFs were increasingly specialized in particular fields and techniques and, with few exceptions, they were stuck in specific cognitive /research niches. The reason this specialization worked counter to becoming a fully integrated pharmaceutical company is that the process of drug discovery (and development) still requires a broader and more “general” perspective, which integrates several. This broader perspective is necessary on many fronts, including alternative routes to the discovery of particular classes of drugs, the cognitive complementarities among different techniques and bodies of knowledge, and the realization and exploitation of economies of scope.

Indeed, later generations of NBFs (and the new “stars” like Affymax, Incyte and Celera) were largely created on the basis of specialization into radically different new technologies like genomics, gene therapy, combinatorial chemistry and what is now called “platform technologies”. These technologies are essentially research tools and the companies developing them do not aim to become drug producers, but providers of services to the corporations involved in drug discovery and development. As argued for example by Steve Casper and Hannah Kettler (YEAR), these companies are characterized by radically different risk profiles, having a potentially larger market and avoiding problems of conducting clinical trials. They may thus be able to sell specialized services to a wider range of potential buyers - which would generally be other companies rather than the end user patients / doctors.

This outline of the changing fortunes of NBFs allows us to see some of the relative strengths and weaknesses of NBFs as compared to integrated pharmaceutical companies. Collaboration allowed NBFs to survive and - in some cases - to pave the way for subsequent growth in many respects. First, clearly, collaboration with large companies provided the financial resources necessary to fund R&D. Second, it provided the access to organizational capabilities in product development and marketing. Established companies faced the opposite problem. While they needed to explore, acquire and develop the new knowledge, they had the experience and the structures necessary to control testing, production and marketing. Both companies also wanted collaboration with the relevant basic scientific communities, in order to gain access to new sources of knowledge.

3.2.2 The adoption of molecular biology by established companies

Indeed, large established firms approached these new scientific developments mainly from a different perspective, i.e. as tools to enhance the productivity of the discovery of conventional “small molecule” synthetic chemical drugs. These differences help explain why the large established pharmaceutical firms have not been overtaken by the specialized biotechnology firms - and have instead found specialized and complementary roles within the system.

For the large pharmaceutical firms, the tools of genetic engineering were initially employed as another source of "screens" with which to search for new drugs. Their use in this manner required a very substantial extension of the range of scientific skills employed by the firm; a scientific work force that was tightly connected the larger scientific community and an organizational structure that supported a rich and rapid exchange of scientific knowledge across the firm (Gambardella, 1995; Henderson and Cockburn, 1994). The new techniques also significantly increased returns to the scope of the research effort (Henderson and Cockburn, 1996). In turn, this required the adoption of organizational practices and incentive structures which in some way attempted to replicate some of the typical characteristics of an academic environment. According to Cockburn, Henderson and Stern (1999), the new organization of R&D implied "new mechanisms for monitoring and for promotion, different ways to organizing researchers into teams, recruiting new types of human capital, and different types of interactions with researchers external to firm".

In fact, the molecular biology revolution made innovative capabilities critically dependent on publicly generated scientific research. Far from being a costless and direct process, the major changes in the knowledge base during this third epoch have implied that companies had to establish much closer and tight linkages with the scientific community, in various forms: research contracts, long run funding agreements to particular teams or institutions, etc. This required firm investment to monitor and maintain networks for potential sources of information.

But a necessary condition for getting access to such knowledge, both from a cognitive and a sociological perspective, was that companies had to become active players in the scientific arena and not simply passive observers and users (Rosenberg 1991). In fact, the relation between firms and public research "is very much a bidirectional one, characterized by the rich exchange of information in both direction" (Cockburn and Henderson, 1998). In other words, companies had to build in-house competencies for at least three reasons. First, in order to develop the "absorptive capabilities" necessary to understand the scientific progresses taking place in academia and in the NBFs. Second, in order to get the "ticket of admission" to the scientific community. Third, because the development of new drugs required not simply the availability of specific techniques, but the evaluation and testing of alternative approaches and the integration of different techniques, scientific disciplines, etc. Finally, it is important to emphasize that, for all these motives, the research capabilities built inside the firm need to be at the leading edge.

As a consequence, companies had first of all to recruit high-level researchers and to publish important papers in scientific journals. In turn, this implied the need to introduce appropriate incentives for attracting (and keeping within the company) such star scientists. This led, for example, to the adoption of "pro-publication" incentives (Cockburn, Henderson and Stern, 1999).

The new research techniques implied also permanent exchange of knowledge within the firm and across different stages of the process of drug discovery (Henderson, Orsenigo and Pisano, 1999). They implied also a much closer interaction between discovery, development and clinical trials (Lamoreaux and Galambos, 1997). This result, as well as a better control of the various activities, was obtained through the implementation of new tools for the assessment and the supervision of research activities.

As several authors have documented (Gambardella 1995, Henderson and Cockburn 1996, Galambos and Sturchio 1997 among others), there was enormous variation across firms in the speed with which the new techniques were adopted. In particular, Rebecca Henderson (1994) has shown that the adoption of biotechnology was much less difficult for those firms who had not made the transition from "random" to "guided" drug discovery. In general the larger organizations which had indulged a "taste" for science under the old regime were at a considerably advantage in adopting the new techniques. On the contrary, smaller firms, firms that had been particularly successful and the older regime and firms that were much less connected to the publicly funded research community were much slower to follow. The embodiment of the new knowledge was in any case a slow and difficult process, because it implied a radical change in research procedures, a redefinition of the disciplinary boundaries within laboratories and, in some cases, changes in the divisional structure of the company as well. Collaborative research with the NBFs and with universities allowed these companies, in many case, to get access to the new technology and to experiment in alternative directions. The advantages stemming from these interactions could be fully exploited however only through the contextual development of in-house capabilities, which made it possible to absorb and complement the knowledge supplied by external sources (Arora and Gambardella, 1992). Collaboration with universities, NBFs and internal research were indeed strongly complementary.

3.2.3 The network of collaborative relations

As a consequence, the SSI was transformed by the emergence of a new organizational form, namely the network of collaborative relations. Indeed, a dense web of collaborative relationships emerged, with the start-up firms positioned as up-stream suppliers of technology and R&D services and established firms positioned as downstream buyers who could provide capital as well as access to complementary assets.

One finds in the literature widely different interpretations of the nature, motivations, structure and functions of these networks, ranging from more sociologically oriented approaches to economic explanations based on (various mixes of) alternative theoretical backgrounds, e.g. transaction costs, contract theories, game theory and competence-based accounts of firms' organization.

According to an influential interpretation, the role played by scientific knowledge in pharmaceutical research is stressed and the nature and properties of the learning processes fuel the emergence and evolution of networks. In this vein, collaborations represent a new form of organization of innovative activities, which are emerging in response to the increasingly codified and abstract nature of the knowledge bases on which innovations draw (Arora, Gambardella, 1994; Gambardella, 1995). To be sure, substantial market failures exist in the exchange of a commodity like information. However, the abstract and codified nature of science, coupled with the establishment of property rights on such knowledge, makes it possible, in principle, to separate the innovative process in different vertical stages. Thus, the innovative process can be adequately represented as a sequence going downstream from science to marketing, in which division of labour can occur at any stage of the process. Different types of institutions tend to specialize in the stage of the innovative process in which they are more efficient: universities in the first stage, small firms in the second, big established firms in the third (see also Arrow, 1983). In this view, then, a network of ties between these actors can provide the necessary coordination of the innovative process. Collaborations are likely to be a permanent feature of the industry, with a large (and possibly continuously expanding) number of entities interacting with an equally large number of other entities, generating an intricate network within which each subject specializes in particular technological areas or stages of the innovative process getting benefits from an increasing division of innovative labor.

According to another interpretation, collaborative relations are instead considered as a transient phenomenon, bound to decrease in scale and scope as the technology matures and as higher degrees of vertical integration are established in the industry (Pisano, 1991).

Finally, according to some more radical interpretations, the complex and interdisciplinary nature of relevant knowledge bases in pharmaceutical R&D tends to make technological innovations the outcome of interactions and cooperation among different types of agents commanding complementary resources and competencies (Sharp, 1985; Orsenigo, 1989; Pisano, 1991; Pammolli, 1996). In this perspective, it has also been suggested that the locus of innovation (and the proper unit of analysis) is no longer a firm, but a network of differentiated agents (see Powell, Koput, Smith-Doerr, 1996). In this case, the direction of causation is reversed: it is the structure of the network and the position of agents within it that fundamentally determine agents' access to relevant sources of scientific and technological knowledge and therefore innovative activities and performances (see also Kogut et al. 1994; Walker et al., 1997).

The network of collaborative research and the emergence and development of a vibrant market for technology have certainly become a typical characteristic of the bio-pharmaceutical

industry. The ability of the firm to access and make efficient use of such network of collaborative relations and of the underlying market for technology have become an important source of competitiveness. Participation to the market for technology allows companies to get access to external knowledge and to increase the productivity of their research. For example, empirical studies on the rates of success and failures of projects carried on entirely in-house as compared to projects involving the acquisition of licenses from third parties show that indeed licensed projects have higher probability of success (Gambardella, Orsenigo and Pammolli, 2000; Gambardella, Pammolli and Riccaboni, 2000). For conflicting evidence, see Pisano, 1997).

Indeed, the formation and development of the network was certainly facilitated by the partly "scientific", i.e. abstract and codified nature of the knowledge generated by the NBFs (Arora and Gambardella, 1994, Gambardella, 1995). In this sense, the new firms certainly acted as "middlemen" in the transfer of technology between universities -- which lacked the capability/willingness to develop or market the new technology -- and established pharmaceutical firms that lacked technical expertise in the new realm of genetic engineering but that had the downstream capabilities needed for commercialization.

However, this is only part of the story. First of all, it is worth noting that collaboration does not simply involve the transfer of knowledge from a NBF lacking complementary assets to an established corporation that uses such knowledge to develop and market the drug. Collaboration takes place mainly in the pre-clinical stage rather than in the marketing stage and usually an established corporation strikes different agreements with different NBFs at the same time and within the same project. This confirms once again not only that external R&D is never a substitute, but it is strongly complementary to in-house R&D (Cohen and Levinthal, 1989; Arora and Gambardella, 1992). Even more important, the innovative process involves the effective integration of a wide range of pieces of knowledge and activities, which are not ordered in a linear way and that may not be easily separated (Orsenigo, 1989). Thus, the processes of drug discovery and - a fortiori - drug development require the integration of different disciplines, techniques, search and experimental procedures and routines, which are not generally separable and codified. And substantial costs still remain in transferring knowledge across different organizations, especially for the tacit and specific component of knowledge.

Moreover, the access to the network of collaborations and to the market for technologies is not unrestricted. On the contrary, the network of collaborative relationships itself tends to consolidate and to become increasingly hierarchical. Indeed, the network has been continuously expanding over time, mainly through the continuous entry of new, increasingly specialized, firms collaborating with large incumbents. Despite this growth, however, the network tends to consolidate

around a rather stable core of companies. This core is essentially composed by large incumbents and early entrants in the network. This suggests the existence of first-mover advantages even in the network of collaborations, which becomes increasingly difficult to enter as time goes by and can be perturbed only and temporarily by new major technological discontinuities (see Orsenigo, Pammolli, Riccaboni, 2001).

In this perspective, the emergence and subsequent evolution of the network of collaborative relations in the third epoch can be analyzed as an adaptive response to the emergence of a radically new knowledge base - molecular biology – the properties of which and of the related learning processes contributed to shape the network of relations among firms and more generally the patterns of industrial organization. As discussed in Pammolli (1996) and in Orsenigo, Pammolli, Riccaboni (2001), scientific progress did not only simplify the search space by providing more general theories. It also led to an explosion of the search space, with a continuous proliferation and branching of hypotheses and techniques at increasing levels of specificity. In a context of rapid and tumultuous technological advance, where knowledge is still fragmented and disperse, no single institution is able to develop internally in the short run all the necessary ingredients for bringing new products on the marketplace.

Each NBFs, in effect, represents a possible alternative approach to drug discovery and a particular instantiation of the opportunities offered by the progresses of science. The high rate of growth of knowledge, its branching into increasingly specific and uncertain directions and.- after 1992 - the appearance of platform technologies led to the generation of a wide variety of approaches and lines of research. The large established corporations and some of the companies belonging to the first generations of NBFs operated instead at a “higher” level of generality and “tested” the new hypotheses/ techniques embodied by successive generations of NBFs. They also act as integrators of differentiated and strongly specialized fragments of knowledge in broader projects and portfolios of projects in pharmaceuticals.

These properties of the knowledge base and of the related learning processes induced particular patterns of division of labour between different types of firms. In general, the results indicate that two different logics of exploration and technological advance co-existed and were strongly complementary in the evolution of the network. One followed a trajectory of increasing specification of general hypotheses. The other progressed towards the development of platform technologies. The first trajectory generated patterns of division of labour in which older generations of firms worked at higher levels of generality and linked with successive generations of new entrants, who typically embodied increasingly specific hypotheses and techniques. The second trajectory induced instead collaboration between all types of firms, modifying the inter-generational

structure of the agreements typical of the first trajectory. In other words, several mechanisms influenced division of labour and they interacted dynamically to produced quite complex patterns.

In both cases, however, incumbent firms were able over time to absorb the new knowledge and turned to the youngest entrants to get access to the newest techniques. Thus, the expansion of the network was mainly driven by the entry of new agents embodying new techniques. At the same time, the network tended to take a distinct hierarchical structure, with different firms operating at different levels of generality, which was perturbed but not broken by transversal techniques.

As a result, large established corporations were not wiped away by the new entrants, but were able to maintain industry leadership. They were able to gradually absorb the new knowledge and to build organizational structures capable of efficiently managing and integrating the complementarities in the production and use of knowledge as well as keeping control of the relevant complementary assets. As Gambardella, Pammolli and Riccaboni (2000) have shown, large corporations do not seem to be characterized by any absolute disadvantage in the process of discovery: if anything the reverse seems to be true. So, division of labour emerges rather from the comparative advantage that big firms have in drug development as compared to NBFs and from the tumultuous rate of technical change, which spurs continuously new waves of innovations from every quarter.

All this supports two hypotheses already advanced in the literature, namely a) the cumulateness of learning and competence building processes (see Henderson, Orsenigo, Pisano, 1999) and, b) the significant capabilities by established multi-technology R&D intensive corporations to absorb new knowledge and techniques generated outside firms boundaries, despite major technological discontinuities and breakthroughs resulting in the growth of specialized technology producers. (Cohen, Levinthal, 1989; Henderson, 1994; Cockburn, Henderson, 1996; Granstrand, Patel, Pavitt, 1997, McKelvey 1996).

3.2.4 The other face of division of labour: M&A

Contextually to the processes of division of labour and to the emergence of the network of collaborative relations, another – seemingly conflicting – phenomenon is characterizing industry evolution, namely the intensification of the processes of mergers and acquisitions. M&As occur at all levels: between NBFs, between large firms and NBFs (as in the case of Hoffman-La Roche and Genentech), but above all among the giants of the industry.

Indeed, ever since the early Eighties a wave of mergers has sustained increasing levels of concentration within the industry. Several reasons may account for this trend.

First, the rising costs of R&D and marketing imply larger markets and rationalization of the portfolio of products. Given the enormous amount of resources needed to bring a drug to the market

and to sustain it afterwards, only very large organizations can sustain these efforts. Second, mergers can be justified by the need to complement the research and market portfolios, acquiring new competencies and attempting at exploiting economies of scope in R&D and marketing. Third, M&As might be triggered by declining competitiveness, exhaustion of the pipeline and expiration of patents on crucial products. Fourth, M&As can occur on rather conventional grounds for strategic purposes, e.g. to eliminate competitors. Fifth, as we shall discuss again later, mergers take place through vertical integration downstream, through the acquisition of distributors. Sixth, large corporations acquire producers of generics, either to preempt competition on their brand product in specific markets or to apply strategies of market segmentation, producing both the branded good at high prices and the generic version at lower prices.

The available literature provides little evidence so far on the relative role of these factors, let alone on the technological and economic outcome of M&As. If anything, casual empiricism suggests questions rather than answers. In many instances, M&As seem to respond mainly to “defensive” motivations, in that they involve “weakening” European companies (e.g. Ciba Geigy and Sandoz forming Novartis, Rhone-Poulenc and Hoechst forming Aventis, Astra and Zeneca merging into AstraZeneca) trying to reach some ill-defined “critical mass” or to acquire a new pipeline as important patents are bound to expire (Glaxo and Smithkline –Beecham). In other cases, it is successful American corporation that acquire weaker European companies. It would appear, however, at a first sight, that the stronger American companies (like Merck or Pfizer) are less involved into this type of expansion than weaker US corporations or European firms.

The processes of M&A are relevant also because they usually involve the relocation of research in specific geographical areas, like the UK and Ireland and, especially, the USA. Thus, this trend is likely to be changing the geography of innovation, probably strengthening the existing leads and lags and creating stronger concentration in R&D activities.

In any event, what seems particularly interesting in this trend is that these processes of vertical and horizontal integration take place jointly with seemingly opposite processes of division of labour in innovative activities. Despite the difficulty of accurately identifying and measuring the economies of scale and scope that are likely to motivate M&As, this observation strengthens the intuition that technological and institutional change does not simply induce unequivocal incentives towards division of labour and the creation of markets for technology, but it modifies the very space where complementarities and the boundaries between markets and hierarchies are defined as well as their very nature.

3.3 Institutional preconditions and their changes: mixing organizational and selective principles

The transformations we have been describing so far in the organization of firms were accompanied by other profound changes in the Sectoral System of Innovation. Such changes were particularly important in the USA and indeed they are often considered as a fundamental explanation of the emerging American leadership in pharmaceuticals. Some of these changes pre-date the molecular biology revolution and constituted a precondition for the following developments. Other changes are best understood as adaptive responses to the scientific revolution. Moreover, other transformations occurred that are largely exogenous to the R&D process but influenced profoundly the evolution of the sectoral innovation system.

First, new agents – beside NBFs – acquired a prominent role: the venture capital industry, the scientists, universities and Offices for Technology Management; the patent offices and the Courts, etc. Second, again the relationships among these agents changed in their nature and led to the mixing of different organizational and selective principles. In general, the patterns of division of labour and the structure of complementarities among agents and functions underwent a drastic reconfiguration.

Such changes are important because they imply that previously separate agents began taking on intertwining roles in the changing sectoral system of innovation. The transformations implied a blurring of the boundaries as well as new roles for some agents. In particular, universities - and university scientists - went from a position of providing basic research and of commercialization through NBFs to playing a more direct role in especially intellectual property rights. Likewise, firms could influence their propensity to survive, irregardless of the value of their innovations, based on their access to specialized network resources such as the management and financial skills of venture capitalists. These types of conscious attempts to change the outcome by agents also affected the selective pressures within the sector.

Thus, rather than having individual actors with very specific and specialized roles in the sectoral systems of innovations, there was a broadening of relevant actors and a blurring of roles. In this epoch, individual scientists not only performed basic scientific research, but also had and have significant research linked directly to larger and smaller firms. The development and expansion of venture capital helped drive the expansion of NBFs, especially in the USA.

3.3.1 Industry-University relations, appropriability conditions and venture capital

The development of the biotechnology industry in the USA rested on the concomitant growth of series of supporting organizations and institutions 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).

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 (), 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 licencing 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.

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 favourable 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, Etzkowitz 19xx). 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 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 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, the American system led to a situation of increasingly strong property rights, whereby universities - and individual university scientists - began having more incentives to work on problems more closely related to the concerns of firms and of venture capitalists. If they didn't get a grant, they could always get a patent or start up a company. They could - and many were - even if they were successful researchers. In fact, some research has even indicated that the strongest basic scientists in this sector also had the strongest patents (Zucker et al). Assuming that basic scientific work also maintained autonomy, this implies that individuals and organizations have been increasingly involved in dual selection environments. On the one hand, most are still involved in pushing forward the frontier of basic science. On the other hand, many are also involved in the search for and in the development of economically profitable ideas, either directly through patents and companies or indirectly through future wages.

The third pillar of this emerging system was of course venture capital. Once again, venture capital was a long-standing institution in the American financial and innovative system. It was already active – in various forms – ever since the 1920s (or even before) and emerged as a vibrant industry with the electronic revolution in the 1960s. We won't re-discuss here the history and the role of venture capital, nor its embeddedness in the unique structures of the Anglo-Saxon systems of

finance, corporate governance and labour markets. In the present context, it is perhaps worth just stressing how venture capital performs a crucial role of bridging and complementing different constituents and roles within the “new” system of bio-pharmaceutical innovation.

Venture capital provides first of all finance to prospective academic entrepreneurs. In this function, the venture capital industry is strictly dependent on – and contributes to further strengthen – a tight appropriability regime, since patents are the fundamental collateral – or means for NBFs. Second, venture capital does not only or simply provides finance but also and perhaps even more important managerial advice and organizational capabilities. Contrary to the conventional stereotype of the American financial institutions, venture capitalists are characterized by an extremely strong “hands-on” and “long-run” approach towards the companies they are financing.

In this function, venture capital does not only or simply bridge science and markets. To perform this function, venture capitalists need strong specific and technical capabilities not only in finance but also a deep knowledge of the science and the technology in which they are investing. Thus, a significant number of PhDs in biology end up working in venture capital firms and venture capitalists have to be part of the same network of conferences, literature, scientists, etc. Thus, venture capital mixes technology, academia and finance. Once again, the overlapping of these realms is not always easy and frictionless. In some cases, financial considerations lead to accelerated IPOs that threaten the process of construction and consolidation of technological and organizational capabilities of the companies.

In summary, the 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 both to understand the similarities and differences between European and American pharmaceuticals and to further develop the analysis of sectoral systems of innovations.

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

Second, this system is highly decentralized and fragmented, 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, as we shall discuss in more depth later on, in 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..⁷

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, what is particularly interesting is that these trends are not simply interpretable –as conventional economic theory would suggest – either as a process of deepening division of labour among agents on the basis of their comparative advantages, or as processes of vertical and horizontal integration. Indeed, as we noted previously in relation to the NBFs, this is certainly an

⁷ This fascinating history is told and discussed by Rebecca Eisenberg (199x)

important part of the story. However, it's only a part. First of all, it is worth noting that division of labour and processes of integration are taking place at the same time. What is perhaps even more important is that agents are changing their roles and functions, redefining their position in a new network. In other words, the space in which division of labour was previously defined, is not the same any longer and is constantly changing. Thus, rather than specializing in their "core activities"- teaching and research - universities are diversifying "downstream" into the commercial exploitation of their main product and to this task they are creating new organizational forms (and new incentive mechanisms, new selective principles). NBFs do not simply pick up knowledge created at universities, develop it into commercializable products for sale to large pharma corporations, functioning as an intermediate stage in the production process. They also take a function of integrators of different types and fragments of knowledge, embody different roles and different incentive structures, devising once again new organizational structures to support these tasks. Many NBFs are founded with the aim of becoming in the future large integrated pharmaceutical producers. But , given the organizational and financial constraints, they often become specialized suppliers of specific techniques and research projects. In the process of experiencing this transformation, the principles on which projects are selected and developed, the financial strategy etc., obviously change as well. Large corporations internalize some basic principles of academic research into the organization of their laboratories and in the incentive structure of their researchers.

Thus, these developments present an important challenge to economic analysis. One set of questions has to do with the conditions at which different selective mechanisms and principles can coexist and co-evolve. The most prominent example is obviously given by the potential conflict or virtuous cycle between the selection mechanisms typical of the commercial sphere and of the academic world (Dasgupta and David, 1994 ; Mazzoleni and Nelson, 1999 ; Mowery...). To what extent it is possible for individuals to balance the demands of both selection environments ? And to what extent do commercial pressures tend to dominate other ones ? Both are serious questions for the future of this sectoral system of innovation, because the answers could have serious implications for the future innovation opportunities. If biotechnology-pharmaceuticals relies on basic research as a source of profitable new ideas - and much research suggests this is the case, then pressures which diminish that momentum and/or change it into other directions may be quite disastrous. It could be like killing the goose which lay the golden eggs. In the longer term, these clusters of firms are reliant on the basic science - yet in the short term, they need more immediate feedback, skilled personnel, etc.

In addition to the increasing number and extent of intellectual property rights, there are increasingly pertinent questions about ownership over biological material like blood samples and DNA which will affect the future potentials. On the one hand, some of this information is only valuable if someone collects and analyzes a large sample while on the other hand, some of the material is in itself very valuable, given certain modifications. New firms are being started to try to exploit these possibilities - sometimes with success and sometimes with criticism.

One of the critical issues is thus the extent to which open science is - or is not - still occurring. The selection environments are changing at such a rapid pace, that the blurring of actors and of boundaries for selection are creating a novel situation. Interestingly enough, this blurring of boundaries seems to imply that the same individual - and same organization - has greater scope for moving between activities. In some cases, the persons themselves move - or are involved in more than one activity. A university professor may be head of a company R&D effort, to later return to a university. In other cases, the organization as a whole may engage in a variety of activities, as when universities promote basic science and intellectual property rights. In yet other cases, the intense flows of contacts and knowledge between different actors like universities, venture capital, established companies and NBFs is based on both market and non-market based interactions which stimulate new forms of innovation.

In a somewhat different but related perspective, one might consider that that these process of “hybridization” of organizational forms and selective principles may on the one hand lead to the organizational and institutional innovation; but on the other extent, 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 labour 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.

3.4 Changes in demand and in regulation

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 behaviour 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 creating or strengthening new agents, ties among agents, etc.. Once again, the patterns of development of the sectoral system were quite different across countries.

3.4.1 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 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, 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.

3.4.2. 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 is increasingly perceived as a fundamental human right and/or in some cases as a public good⁸. Thus, decreasing public coverage of pharmaceutical expenditure is sometimes 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 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 behaviour 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.

Demand control policies have met an increasing consensus, at least in terms of their utility if not about the concrete forms to adopt, than intervention on the supply side like price controls.

⁸ 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 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).

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 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, at least in the short run, relatively effective in containing expenditure growth. However, expenditure patterns tend to rapidly return on the long run trend.

Moreover, 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.

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 government is anyway the largest 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 an employer 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 on 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 distortive instrument for purposes of cost-containment. While the argument is quite complex, it essentially relies on the observation that reductions in price go along with 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 doctors⁹. Today generics are estimated to account for more than 50% of drug prescribed (in volume). CHECK SOURCE Moreover, the rise and 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

⁹ The same Act provided a "restoration" of patent duration to take into account delays in the approval process.

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 behaviour, 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 the 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.

3.5. The Decline of European Competitiveness

There is substantive evidence that in the Age of Molecular Biology and Cost Containment, the European industry started to lose competitiveness vis-a- vis the USA. The failed take-off the “biotechnology segment” of the industry has often been taken as the main manifestation and reason of this decline. However, it is important to notice that other factors have played an important role. For example, we already noted that large corporations have reacted more slowly to the new technological regime. Moreover, the European industry appears to be in general less efficient than the American one.

A recent report to the European Commission (Gambardella, Orsenigo and Pammolli, 2000) documents that:

- a) in the 1990s the European industry has grown less and it is much more labour-intensive than the US industry.
- b) The sales of major innovative products by the US multinationals have increased more significantly than those of the European multinationals in the 1990s. Moreover, European big corporations seem to lag somewhat behind in their ability to produce and above all sell, new, innovative, best selling drugs. The observed differences in sales growth between European and US largest multinationals during the Nineties do not seem to depend only on differences in the ability to develop new breakthrough drugs, but also on the observed difference in demand growth between the two areas.
- c) The 1990s have shown an acceleration of the competitiveness of the US pharmaceutical industry as a whole especially in the innovation-intensive segment of the industry. The leading US firms have a higher share of turnover based on recent products compared to the European

firms; have a higher share of patents in the new biotech fields compared to “classical” pharmaceuticals; are a preferred destination of research by the European companies as well.

- d) The competitive advantage of the US companies in innovation relies both on higher internal capabilities but also on a higher reliance on collaboration, especially in the pre-clinical stages of research and development. More generally, the US exhibit a more pronounced division of labour in the drug innovation process between large companies on the one hand and small biotech/specialised firms as well as scientific institutions on the other.
- e) The US advantage and the deteriorating competitiveness in Europe have been emphasised and deepened by the advent of the molecular biology revolution. The competitiveness of the US system seems to be largely related to the extensive exploration of new technological opportunities. In fact, one notable difference between Europe and the US in the 1990s is that while the US have become the centre of world basic research in life sciences and have continued the development of a new research-intensive industry in this field, Europe has been unable to develop and attract research and to complete the process of vertical specialisation in the most innovative areas of the drug sector. Particularly, Europe has not really given rise to a full fledged industry of innovation specialist companies and technology suppliers like in the US.
- f) However, the declining competitiveness of the European industry appears to be linked not only – or not even mainly – to a worsening performance of the largest corporations, but also to the persistence of a large fringe of smaller, inefficient companies. In particular, in some European countries there seems to be too little domestic competition that tends to nurture inefficient positions within the industry. Price fixing mechanisms tend to protect local firms in domestic markets, allowing for the survival of infra-marginal, high labour-intensive companies.
- g) However, the decline in European competitiveness in pharmaceuticals and biotechnology is not a homogeneous phenomenon, but it actually results from largely heterogeneous performances of individual firms and countries. To a considerable extent, the European problem derives from the deterioration of the German and Italian performance. Conversely, the cases of the UK, and in the 1990s of Denmark, France, Sweden and Ireland, have to be considered as success stories.

Several interacting factors might contribute to explain these trends and these factors have acted at different levels. In general, we suggest that the relative EU decline within this industry is largely determined by what happened in the pre-molecular biology/cost containment transition era. When it arrived, “Europe” was not able to react as quickly and efficiently as the USA, due to a combination of factors, which can be summarized in the sluggishness in redesigning a more complex system and in redefining complementarities and division of labour. This means that the American path led to a much faster and more profound blurring of the roles of actors, rise of new

actors, and increasing complexity of networks in order to develop and exploit knowledge economically. Within Europe, these trends occurred more slowly and seemed to have involved a lower number of new actors - or rather, some of them went to the USA to access the appropriate new forms.

Here, in order to articulate this conjecture, we focus on four sets of variables that, in various ways have been indicated as important in affecting the diversing trends of the American and European industries, namely:

- a) the size and structure of the biomedical education and research systems;
- b) Some basic institutions governing labour markets for skilled researchers and managers, as well as corporate governance and finance;
- c) Intellectual property rights and patent law;
- d) The nature and intensity of competition on the final market.

3.5. 1 Education and Research in Biomedical Innovation Systems

We mentioned already that both the absolute levels of investment in biomedical research and the structure of the research systems were crucial factors in explaining the American leadership in life-sciences. Here, it is worth emphasizing other factors that particularly important in the Age of Molecular Biology.

First, the structure of the funding system and the strategies of the funding agencies are crucially important. In the USA, most of the funding is administered through the NIH, with: a) a substantial integration between the production of biological knowledge on the nature and mechanisms of human diseases, clinical research, medical practice, and the discovery and development of new therapeutic treatments; b) a significant support towards basic or fundamental science in universities and public research centres, widely disseminated through publication in the refereed literature. Moreover, the American system is characterised by a variety of sources of funding and selection mechanisms, which complement the role of the NIH and act – always starting from scientific excellence – according to different allocative principles (See Braun, 1994; Mowery, 1998; Stokes, 1997, and Guston in Branscomb, Keller, 1998). All in all, the US research system achieves efficiency through competition among research units. At the same time, it allows diversity to be explored and institutional flexibility to be achieved. In Europe, as we already noted, funding has tended to be administered mainly at the national level, with strongly differentiated approaches and wide differences across countries. In many cases, resources have either been spread among a large number of “small” laboratories, or they have been excessively concentrated in the few available centres of excellence. Funding coming from the various European programmes has only partially changed the situation (Pavitt, 1998).

Thus, 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 constitutes a fundamental difference. Moreover, 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 recently become a standard part of the curriculum of pharmacologists, pathologists and medical consultants. Research has tended to be confined into highly specialised laboratories in universities and especially in public research centres, with little interaction with teaching, medical practice, and industrial research.

Also for these reasons, large European companies have been in general more sluggish in adopting molecular biology as compared to their American competitors. Particularly, the European firms have remained for a longer time more closely linked to the cognitive and organisational procedures that governed research when chemistry constituted the main knowledge base.

This has produced a vicious circle that has made the entry of the new biotechnology companies more difficult. In the first place, there is evidence showing that rates of formation of new start-ups are strongly correlated with the strength of University and public research institutes in the underlying sciences (Zucker, Darby, Brewer, 1997)

Moreover, given the delay in the adoption of molecular biology by the large companies in Europe, new prospective start-ups lacked an essential source of survival and growth, through the establishment of collaborative agreements. In the absence of such competencies, the large European companies turned to the American scientific and technological base to tap and absorb the new requisite competencies during their catching-up process. Indeed, several studies, show that large European multinationals have tended to establish agreements with research centres and biotech companies in the USA rather than in Europe. Finally, given the fast rates of progress of the scientific and technical knowledge, European start-ups would be often pre-empted by American companies.

In sum, the organisational structure and the internal institutional diversity of the public research system in the USA has promoted (both in terms of incentives and in terms of organisational capabilities) the commercial exploitation of academic research, mainly through the formation of new, specialised companies. The flexibility of the American academic system, the high mobility of the scientific labour market and, in general, the social, institutional and legal context that made it relatively straightforward for leading academic scientists to become involved with commercial firms, have been major factors in the development of the new industry

The willingness to exploit the results of academic research commercially also distinguishes the US environment from Europe. Differently from the USA, 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 organisational 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.

3.5.2 Financial Markets, Corporate Governance, and Labour Markets for Skilled Researchers and Managers.

It is often mentioned that the take-off of biotechnology in the US, both through the large established corporations and the new biotechnology firms (NBFs), owes much to some specific institutions and attitudes that are typical of the American environment and much less developed in Europe. These factors have to do with the structure of financial markets, corporate governance, and labour markets for skilled researchers and managers. The development of venture capital, for example, rests critically on the nature of ownership and contract law typical of the US, which can be used to create sophisticated legal structures used to support risky new ventures.

An important feature of the American institutional environment, which has favoured the development of NBFs and the fast restructuring of big pharmaceutical corporations, is the existence of an active labour market for scientists, technicians, and managerial experts within biotechnology. For example one firm fails or decided to shed competencies in one area, employees must be able to obtain similar employment without severe loss of salary or status. Top executives at start-up firms typically come from large pharmaceutical companies or University research laboratories. These often senior scientists/managers would hesitate in making the move to a start-up if the career risk of doing so were large. Furthermore, innovation is dependent on the flow of knowledge between University labs, start-up research firms, and large pharmaceutical firms. While joint research projects, strategic alliances, and so forth, facilitate this exchange of knowledge, these “network externalities” are also supported by the rapid movement of scientists and technicians across firms.

Thus, if the labour market did not support extensive lateral career mobility across firms, these network externalities would be difficult to sustain (Soskice, 1997; Casper, Kettler, 2000).

As discussed by Soskice (1997) and Casper and Kettler (2000), in Europe, the organisation of labour and company law, combined with the organisational strategies of most large companies and with the structure of the academic labour market, constrains the development of US-style active labour markets, and make it harder for companies to “hire and fire” personnel or rapidly cut non-performing assets. Moreover, though there is often some lateral movement across firms very early in a person’s career, the vast majority of European employees build their own careers within one firm. Correspondingly, the structure of decision-making, remuneration, and career-paths within firms and universities differ fundamentally from common practice within the United States or United Kingdom. Career paths tend to be well specified, incremental, and based on rank hierarchies. This structure of large company organisation works quite well in industries dependent on long-term investment strategies in relatively stable technologies, characterised by the diffusion of deep skills throughout the firm. In particular, it encourages the creation of tacit organisational knowledge throughout the firm that enhances flexibility. However, this system creates fundamental obstacles to the creation of high-risk technology start-up firms. The risk of a «jumping ship» from an established large company (or – though there is less research in this area – a prestigious University professorship) to a start-up firm is extremely high (Audretsch, Stephan, 1996; Powell et al., 1996; Zucker, Darby, Brewer, 1997).

More generally, successful research in high-technology firms requires the recruitment of scientists with highly specialised knowledge. In the US, this problem is partially dealt with through a market-based system of financial institutions and through very strong financial incentives, typically stocks options. In Europe, this area is undergoing extensive change during the late 1990s, but during the 1980s the organisation of the European financial markets and property rights law made stock-based financial systems difficult to implement.

It is commonly believed that lack of venture capital has restricted the start-up activity of biotechnology firms in Europe. There is little question that venture capital played a key role in facilitating the creation of NBFs and of a market for technology in the USA. There are important institutional reasons why the venture capital market is so large in the US. Primarily, in the United States the ownership of firms is primarily financial in structure, and rooted in large capital markets (e.g. NASDAQ, NYSE). Conversely, in many European countries, the lack of developed capital markets for technology firms create important barriers for prospective venture capitalists (Soskice, 1997; Casper, Kettler, 2000).

The forms of corporate governance and the structure of labour and financial markets are therefore likely to have hindered the process of adaptation of the European industry to the technological and institutional shocks. However, direct empirical evidence on these issues is not massive. Moreover, the relevance of these factors might turn out to be somewhat exaggerated. In fact, the observed difference in performance among some European countries may have more to do with differences in institutional settings, drug price regulation mechanisms, the nature of the scientific system, and the like. This suggests that differences in the nature of corporate governance and in the structure of labour and financial markets may have been important but not decisive factors in shaping the patterns of adaptation.

Similarly, as far as venture capital is concerned, there appear to have been in Europe many other sources of funds (usually through government programs) available to prospective start-ups. In addition, although venture capital played a critical role in the founding of US biotechnology firms, collaborations between the new firms and the larger established corporations provided a potentially even more important source of capital. This raises the question: could prospective European start-ups turn to established pharmaceutical firms as a source of capital? As noted earlier, European large corporations have collaborated relatively more with US biotechnology firms. Even in the absence of other institutional barriers to entrepreneurial ventures, start-ups in Europe might have been crowded out by the large number of US based firms anxious to trade non-US marketing rights for capital. Given the number of US NBFs in search of capital, European firms interested in commercialising biotechnology had little incentive to invest in local biotechnology firms.

As a partial support to this interpretation, in several European countries various initiatives by both domestic and foreign investors to launch venture capital funds were attempted in the Nineties, with mixed success so far and often ending up investing in new foreign biotechnology companies. Conversely, foreign venture capital firms have funded some of the few experiences of successful European NBFs. All in all, the slow development of venture capital in Europe seems to depend less on the lack of investors and funds than on the paucity of supply of promising start-ups based on solid scientific research.

3.5.3 Protection of Intellectual Property Rights

We already discussed the role of IPRs in stimulating the commercialization of science and the creation of markets for technology in the USA. In Europe, 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, as we noted earlier, considerable controversy surrounds this issue. 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 favour the creation of markets for technology and hence a faster and more ordered diffusion and use of knowledge (Merges, Nelson, 1994).

3.5.4 Degrees and Forms of Competition on the Final Market

The levels of drug prices as well as the various mechanisms of price regulation used in Europe are likely to have put pressure on pharmaceutical companies and may well have introduced distortions in the competitive mechanisms.

The procedures for the approval of drugs have also played an important role. We already mentioned that the introduction of tougher procedures in this respect contributed to force US and British firms to upgrade their scientific capability. There seems to be a widespread agreement that the less successful performance of other national pharmaceutical industries (like Italy and Japan) reflects much weaker competitive pressures in domestic markets. In these countries, the combination of patent laws, policies surrounding licensing and comarketing agreements, and drug pricing and reimbursement regimes, produced a “soft” regulatory regime whereby firms had little incentive to develop world-class product development capabilities.

The recent trends towards an increasing reliance on market based mechanisms in the effort to control prices and expenditure may start to increase the levels of competition in Europe. However, firms’ strategic orientations and organisational attitudes change slowly and tend to persist for long periods of time. Equally, the development of competencies and innovative capabilities is a long, cumulative and difficult process that does not respond immediately and smoothly to economic incentives.

This consideration is even more important, as soon as it is recognised that behind the differentiated experiences of various European countries there are extremely varied motivations and policy approaches. For example, there is no doubt that the successes of France and Ireland derive from radically different approaches. The latter is largely linked to the creation of an environment favourable to foreign investment, low taxation and little regulation coupled with a strong scientific base. The former is probably the outcome of a revisited form of the traditional French “national champions” policy attitude, with the French research system having been put at the disposal of few large corporations, primarily Rhone Poulenc. Similarly, recent developments in

German biotechnology would suggest that local institutional frameworks can be successfully modified and adapted to the requirements of the technological regimes, without changing their fundamental character (Casper and Kettler, 2000).

4. Conclusions: Linking the Empirical Evidence to Theory

The previous discussion suggests some preliminary conceptual conclusions – or better, conjectures – on why and how pharmaceuticals can be usefully analyzed as a sectoral system of innovation. A first set of conjectures has a “general” nature, in that it possibly refers to the dynamics of different sectoral systems. The second set of hypotheses is specific to the case of pharmaceuticals.

We mentioned at the beginning that at a first, almost simplistic level of analysis, the pharmaceutical industry can be considered as a system or a network because innovative activities involve directly or indirectly a large variety of actors, who know different things, have different incentives and motivations, have different rules of action. We noted also that these actors are linked together through a web of different relationships which include almost pure market transactions, command and control interventions, competition, collaboration and cooperation and all sorts of the so-called “intermediate forms”.

The analysis of the evolution of pharmaceuticals suggests however some further insights.

First, a crucial feature of this industry is certainly that these agents and relations are not simply coexisting, but dynamically they give rise to new agents and forms of interaction. In this particular and possibly extreme case, this process of evolution led to a striking mix and overlapping of different and hybrid forms of learning and selection principles (Mc Kelvey, 1997).

Second, in no meaningful way, this set of relations can be considered as completely coherent and “efficient”. On the contrary, conflict, failures (think of the thalidomide case) and disequilibrium (consider the tension between “open science” and commercial exploitation of fundamental scientific research) have always been a distinctive feature of the industry. At the same time, forms of interaction have been developed that have allowed a remarkable track-record in innovativeness, economic and financial performance and (although not completely uncontroversially) welfare.

Third, the nature and the form of these relationships may also look different when looked at from alternative levels of aggregation or scales of analysis. For example, the above analysis strongly suggests that heterogeneity in firms’ behaviour is a key property of industrial dynamics. Thus, it is important to distinguish between types of firms. The largest corporations have become increasingly international, and hence they respond to a broader range of national selection

environments, including the most stringent ones. They are also able - or pushed - to access knowledge internationally, wherever the relevant market, regulatory or scientific information may be found. The firms which mostly respond to national markets - and thereby mostly react to national institutional environments - appear to be those with the widest range of performance problems. Note, however, as we mentioned earlier, that even firms within the American and/or general Anglo-Saxon selection environment fell into two camps in terms of innovation strategy. There was firstly, a core of innovative firms which were able to combine radical product innovations in-house with incremental product and process innovations through the second epoch. There was secondly, another group of firms which focused more on the mass market and production related innovations rather than the highly novel products. In the transition to the third epoch with the molecular biology revolution, firms reacted very differently, both in terms of time to reaction and in terms of strategy for accessing and exploiting these new forms of knowledge. Moreover, it has been suggested that “communities of practice”, or competence networks, or epistemic communities may be a much more useful concept for analyzing the patterns of innovation in pharmaceuticals rather than firms, especially as new biotechnology companies and the role of specific groups of scientists working at the boundaries between academia and industry are concerned. Finally, in a different perspective, the innovative process proceeds along a series of interrelated phases, each involving different agents and an even more complicated range of relations and feedback among them.

Fourth, the system of innovation in pharmaceuticals has at the same time a firm-specific, a national and a sectoral connotation. For example, it may well be that the declines, recoveries, and take-offs visible at the level of European national industries are due to the decisions of a few large corporations. The smaller countries are especially sensitive to the decisions of the largest corporations. However, it is also clear that national contexts - or combinations of regional contexts - also consist of other types of factors valuable to the firm in its striving to survive and/or innovate. These include factors such as the dominate types of university-industry interaction, the strength of basic science, the moveability and availability of pooled and skilled labor force, availability of venture capital, and the patterns of regulation and competition. However, when the firm is largely bound to a national market, then these factors may be less important than the rate and expectation of future profitability, based on direct pharmaceutical regulation and compensation schemes. In an international world, these types of factors interact in creating various, and specific, environments from which firms may emerge - or be drawn to. This seems to hold particularly in a truly international world, where not only labor, capital, and resources move but also the regulatory aspects and pharmaceutical compensation schemes are becoming increasingly harmonized. In that world, the firm may make different choices about whether to remain national or whether to become

multi-national companies. Hence, in this sense, these factors also affect the propensity of an existing firm to remain rooted to its geographical basis - or to move abroad and become increasingly international

All throughout the paper, we emphasized that there is not only one European case, but a variety of national specificities. Some of the firms have ended up in a type of “local optimum”, which is less efficient than the global best but which worked as long as national institutions, regulation and market rules rewarded certain types of firms. These “local optima” are not, however, stable over the longer term due to the nature of international competition. Therefore, these firms end up being further behind than those firms forced to change and/ or innovate continuously.

Still, there are many aspects of this story which shows strong sectoral specificity, rather than national. In terms of sectoral competition, the markets for pharmaceuticals have been fragmented, both nationally and by product class. In terms of sectoral knowledge flows, the access to appropriate and newly emerging knowledge has been here divided into epochs. While we have shown clear differences between European and American experience, there are also transitions into each epoch which are fundamental and which lie at the sectoral level. In terms of demand and the related issue of regulation, there are also international trends over time at the sectoral level, in addition to national specificities. In general, the trend has been towards more international knowledge (e.g. science-based), more international markets (even if still fragmented at product level) and more international regulation, etc..

Fifth, quite obviously, the sectoral system changes over time. Such change results from different sources. It is spurred by the disequilibria and imbalances that connotate the system. It is driven by external shocks, both “small” ones (as it would be formalized in a dynamic model by the introduction of i.i.d. disturbances) and “big” ones (like the emergence of a new technological paradigm). The process of change is driven also and mainly by the interaction of endogenous learning and selection processes. Agents learn how to improve their position, by developing new techniques, products and marketing strategies. They improve also their ability to use such products and techniques. They learn how to compete vis-a-vis their old and new competitors. They adapt and sometimes try to change to new forms of regulation and forms of markets organization. Mechanisms of selection themselves change. Changes in regulation are just an obvious example. But, even more interestingly, as different selection mechanisms coexist, influence each other and sometimes mix together, the principles of selection become themselves partly endogenous. In fact, they result from the interaction of different mechanisms, from the purposive actions of agents who actively try to change the “rules of the game” and from the disequilibria that at any point in time characterizes the system. Thus, for example, the rise of the welfare state and the expansion of the

markets for drugs led to cost-containment policies. The thalidomide case induced tougher procedures for product approval that in turn changed the costs of R&D, industry structure and the prices of drugs, the competitiveness of firms and national industries.

In a somewhat different terminology, competencies and incentives co-evolve. And it is by no means obvious at the outset what the “right” dynamic mix is, if it exists. Again, as an example, product approval regulations inserted an incentive towards more innovative strategies, at least for those firm and countries which had the capabilities to invest in the new technologies. Similarly, weak patent protection induced imitative strategies, but this effect was much less important for firms and countries which had developed strong technological and scientific capabilities (as for example Germany until the advent of the molecular biology revolution). Conversely, the introduction of stronger patent protection might have contributed to the practical disappearance of the the Italian industry, which was until the mid-Seventies one the more successful producer of generics (Scherer and Weisbrod, 1995). As a final example consider how the molecular biology revolution, by creating new competencies and a new technological regime, induced deep changes in the incentive structures within firms, universities, etc..

Sixth, evolution and adaptation to (internally generated and exogenous) shocks imply processes of restructuring, division of labour, reconfiguration of complementarities. In the language of cognitive sciences, this means identification of new problem decompositions, within and across agents. Thus, as we noted, the emergence of a new knowledge base (molecular biology) implied a new “problem”, new ways and procedures of learning, a new technological regime. The adaptation to the new knowledge base (technological regime) implied a deep reconfiguration of the system : at the firm level (Henderson), at the level of the patterns of division of labour and relationships among firms (through the appearance of new specialized biotechnology firms, the emergence of networks of collaborative relations but also through M&A), at the level of market structure. More generally, scientific progress certainly “simplified” the search space, eliminating certain alternatives that are proven to be wrong (Nelson 1959; Arrow, 1962; David, Mowery, Steinmueller, 1992). However, at the same time, scientific discoveries generated a “deformation” and an expansion of the research space, by suggesting new competing hierarchies of sub-hypotheses as well as previously unconceivable opportunities of discovery. In other words, the opportunities for division of labour and the complementarities between different activities and fragments of knowledge were redefined in a new space, not comparable to the previous one.

Seventh, in this process of adaptation and change, different dynamic processes lead to differential patterns of competition and performances. In other words, we suggest that it is important to look at system dynamics in order to understand structure and performance.

Eighth, within the evolving system, the lack or the weakness of specific competencies, agents or relations between agents decreases overall performance. In other words, competitiveness and performance are a function of the “completeness” and intensity of the relations and on how they are managed.

The European reaction to the Molecular Biology revolution and to the cost containment problem might be interpreted in this way. The new technological regime implied an “explosion” of the search space. “Exploration” has become more difficult, costly and important for pharmaceutical firms. Given the complexity of the space to be searched and the speed at which new hypotheses and techniques are generated, no individual firm can hope to be able explore and to keep control of more than a small subset of such space. Competitiveness increasingly depends on strong scientific capabilities and on the ability to produce and interact with science and scientific institutions in order to explore such an immense and complex problem space. In the USA, this task was accomplished through significant transformations in the vertical structure of the industry, with the emergence of new patterns of division of labour in the innovative process among new and established firm, the development of a market for technology, but also new and organizationally sophisticated forms of interaction among different types of firms and other institutions. The US system was able to evolve, building on some of its typical features, into a highly decentralized but at the same time strongly integrated structure, which appears to be quite successful in combining exploration and exploitation.

In Europe, the lack of strong research competencies in the new knowledge base and the absence or weakness in specific relationships among agents deeply influenced the dynamic path of evolution and the “competitiveness” of the industry. In Europe, the “new problem” was reconfigured and decomposed in a different way as compared to the US case. Europe has been lagging behind in its ability to generate, organize, and sustain innovation processes that are increasingly expensive and organizationally complex.

A similar story seems to apply as it concerns regulation. In many European countries, “invasive” regulation, as it concerns for instance prices, coexisted with a much softer attitude in other domains, e.g. product approval procedures. In many cases, this approach resulted in weak competitive pressures and in the survival of inefficient, marginal firms. The competitive decline of the European pharmaceutical industry appears to have its roots in insufficient degrees of organizational integration and competition within the system, still centred on individual domestic and fragmented research systems and markets.

All this does not imply that the “American way” is necessarily the only and the best way. As we noted several times, the American system is not immune from contradictions and problems. Moreover, past history and inherited institutions heavily influence the patterns of evolution and are

not easily forgotten. In the European case, policies aiming at promoting new biotechnology firms, the proliferation of intermediate institutions for “technology transfer”, an increasing involvement of scientific research in direct commercial activities may be neither feasible nor desirable. The trade-offs between exploration, exploitation, efficiency and equity are intrinsically difficult to resolve and no unambiguous unique “best way” is likely to be definable. Thus, as in any evolutionary environment, there is always the scope for further improvement and change.

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