

# **INNOVATION AND MARKET STRUCTURE IN THE DYNAMICS OF THE PHARMACEUTICAL INDUSTRY AND BIOTECHNOLOGY: TOWARDS A HISTORY FRIENDLY MODEL**

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## ***I. Introduction***

In this paper we present a first version of a “history-friendly” model of the evolution of the pharmaceutical industry and biotechnology.

The motivations underlying this modelling style have been discussed extensively in previous papers (Malerba *et al* 1999, 2001) and we will not come back to this issue here. For the purposes of the present paper, suffice it to say that pharmaceuticals constitutes an ideal subject for history-friendly analysis, for several reasons and especially in comparison to our previous efforts concerning the computer industry.

First of all, it is worth reminding that one of the reasons of interest of history-friendly models consists in the possibility of examining what kind of factors and dynamic processes account for the evolution of different industries. In this respect, pharmaceuticals are radically different from the computer industry.

Pharmaceuticals are traditionally a highly R&D intensive sector, which has undergone a series of radical technological and institutional “shocks”. However, the core of leading innovative firms and countries has remained quite small and stable for a very long period of time, but the degree of concentration has been consistently low, whatever the level of aggregation is considered.

As we shall argue, these patterns of industrial dynamics are intimately linked to two main factors. First, the nature of the processes of drug discovery, i.e. to the properties of the space of technological opportunities and of the search procedures through which firms explore it. Second, the fragmented nature of the relevant markets. Specifically, innovation processes have been characterised for a very long time by low degree of cumulateness and by “quasi-random” procedures of search (random screening). Thus, innovation in one market (a therapeutic category) does not entail higher probabilities of success in another one. Moreover, pharmaceuticals represents a case where competition is less dissimilar to the model of patent races. Understanding if these intuitive factors can indeed explain the observed patterns of industrial dynamics and articulating the mechanisms through which they exert their impact is in itself an interesting challenge. The more so, if this model is compared to the analysis of the computer industry. The comparison might allow for some generalisations about the determinants of the relevant similarities and differences in the patterns of industrial evolution across industries.

A second reason why modelling the pharmaceutical industry is particularly interesting is that this sector is usually considered as strongly science-based. However, science has influenced industrial research in quite different ways over time. Indeed, in the recent past the advent of a new science – molecular biology – has had a dramatic impact on industry structure, the organisation of innovative activities and the competitiveness of firms and countries. Thus, the analysis of the pharmaceutical industry lends itself to a study of a classical and extremely important chapter of the economics of innovation, i.e. the relationships between scientific research and industrial innovation.

Third, the pharmaceutical industry, ever since its inception, has been deeply affected by a large variety of institutional factors and policies, ranging from patents, different forms of regulation (procedures for product approval, price controls, etc.), organisation of the public research systems, etc.. From this perspective, pharmaceuticals constitutes an ideal case for studying the differential impact and the working of alternative policies and national systems of innovation.

In a previous paper (Malerba and Orsenigo, 2001) we began to analyse the dynamics of market structure in pharmaceuticals in the “random screening period”. Moreover, we also performed some

preliminary exercises concerning the effects of alternative patent regimes on innovation and market structure. In this new version of the model, we focus instead on the transition to “molecular biology”. The paper is organised as follows. Section II provides a brief historical account of the evolution of the pharmaceuticals. A particular emphasis is assigned to the discussion of the evolution of the regimes of search of new drugs that have characterised the industry over time.

Section III introduces the main theoretical issues that are raised by the previous historical account and presents the model. Section IV discusses the results and Section V concludes the paper.

## ***II. Innovation and the evolution of market structure in the pharmaceutical industry: an overview***

The patterns of development of the pharmaceutical industry have been extensively analysed by several scholars. In what follows, we rely especially on the work by Chandler 1990 and 1998, Galambos and Sewell 1996, Galambos and Sturchio 1996 and 1998, Gambardella 1995, Henderson, Orsenigo and Pisano, 1999, Mc Kelvey, 1996, Orsenigo 1989, Schwartzman 1976.

In very general terms, the history of the pharmaceutical industry can be analysed as an evolutionary process of adaptation to major technological and institutional “shocks”. It can be usefully divided into three major epochs. The first, corresponding roughly to the period 1850-1945, was one in which little new drug development occurred, and in which the minimal research that was conducted was based on relatively primitive methods. The large-scale development of penicillin during World War II marked the emergence of the second period of the industry's evolution. This period was characterised by the institution of formalised in-house R&D programs and relatively rapid rates of new drug introduction. During the early part of the period the industry relied largely on so called “random” screening as a method for finding new drugs, but in the seventies the industry began a transition to “guided” drug discovery or “drug development by design,” a research methodology that drew heavily on advances in molecular biochemistry, pharmacology and enzymology. The third epoch of the industry has its roots in the seventies but did not come to full flower until quite recently as the use of the tools of genetic engineering in the production and discovery of new drugs has come to be more widely diffused.

### ***II.1 Early History***

The birth of the modern pharmaceutical industry can be traced to the mid-19th century with the emergence of the synthetic dye industry in Germany and Switzerland. During the 1880s, the medicinal effects of dyestuffs and other organic chemicals were discovered. It was thus initially Swiss and German chemical companies such as Ciba, Sandoz, Bayer, and Hoechst, leveraging their technical competencies in organic chemistry and dyestuffs, who began to manufacture drugs (usually based on synthetic dyes) later in 19th century.

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 specialised pharmaceutical producers such as Wyeth (later American Home Products) Eli Lilly, Pfizer, Warner-Lambert, and Burroughs-Wellcome. Up until World War I German companies dominated the industry, producing approximately 80% of the world’s pharmaceutical output.

In the early years the pharmaceutical industry was not tightly linked to formal science. 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.

## *II. 2. The "Random Screening" period*

World War II and wartime needs for antibiotics marked the drug industry's transition to an R&D intensive-business.. With the outbreak of World War II, the U.S. government organised 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. The commercialisation of penicillin marked a watershed in the industry's development. Due partially to the technical experience and organisational 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 and built large-scale internal R&D capabilities. At the same time there was a very significant shift in the institutional structure surrounding the industry. Whereas before the war public support for health related research had been quite modest, after the war it boomed to unprecedented levels, helping to set the stage for a period of great prosperity.

This period was called the golden age of the pharmaceutical industry. R&D spending literally exploded and with this came a steady flow of new drugs. Drug innovation was a highly profitable activity during most of this period. During 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.

The industry's high average level of innovation and economic performance was supported by different interacting factors. One was the sheer magnitude of both the research opportunities and the unmet needs. In the early post-war years, there were many diseases for which no drugs existed. In every major therapeutic category pharmaceutical companies faced an almost completely open field (before the discovery of penicillin, very few drugs effectively *cured* diseases).

Faced with such a "target rich" environment but very little detailed knowledge of the biological underpinnings of specific diseases, pharmaceutical companies developed 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 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 were generally forced to rely 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. Since even the most productive chemist might find it difficult to synthesise more than a few compounds over the course of a week, researchers tended to focus their attention on synthesising variants of compounds that had already shown promising effects in a screen, but that might not be ideally suited to be a drug. Any given compound might have unacceptable side effects, for example, or be very difficult to administer. 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. 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.

Over time, early entrants into the pharmaceutical industry developed highly disciplined processes for carrying out mass screening programs. Because random screening capabilities were based on internal organisational processes and tacit skills, they were difficult for potential entrants to imitate and thus became a source of entry barriers. In addition, in the case of random screening, spillovers of knowledge between firms was relatively small since when firms essentially rely on the law of large numbers, there is little to be learned from the competition.

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. However, the successful introduction of NCEs has to be considered as a quite rare event. Indeed, estimates suggest that, out of all new compounds that were discovered only one over 5,000 reached the market. So, the rate of introduction has been of the order of a couple of dozens per year, and concentrated in some fast-growing areas such as central nervous system, cardiac therapy, anti-infectives and cytostatics. 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' dominate the product range of all major firms" (Matraves, 1999, p.180; Sutton, 1998).

However, entirely new products (New Chemical Entities), only capture a part of innovative activities. "Inventing-around" existing molecules, the introduction of new combinations among them, or new ways of delivering them, etc., constituted a major component of firms' innovative activities broadly defined.

Thus, competition centred around new product introductions but also around incremental advances over time, as well as around imitation and generic competition after patent expiration (allowing a large "fringe" of firms to thrive). Processes of generation of new markets and of diversification across product groups was followed by processes of incremental innovation, development of therapeutic analogues, imitation, licencing. Fast expanding markets allowed for the steady growth of both the first-comer and other early innovators.

The successful exploitation of the economic benefits stemming from innovation required also the control of other important complementary assets, particularly, competencies in the management of large-scale clinical trials, the process of gaining regulatory approval, and marketing and distribution, which also have acted as powerful barriers to entry into the industry.

As a consequence, throughout its history, the industry has been characterised by a significant heterogeneity in terms of firms' strategic orientations and innovative capabilities.

Indeed, ever since its inception, other firms specialised not in R&D and innovation, but rather in the imitation/inventing around, production and marketing of products often invented elsewhere and sold over-the-counter. This group of firms included companies like Bristol-Myers, Warner-Lambert, Plough, American Home Products as well as almost all of the firms in countries like France, Italy, Spain and Japan. Conversely, the "oligopolistic core" of the industry has been composed by the early innovative entrants joined after World War II by few American and British firms, which maintained over time an innovation-oriented strategy. The mechanisms protecting the rents stemming from innovation discussed previously, combined with the presence of scale economies in pharmaceutical research, and marketing may help to explain the dearth of new entry prior to the

mid-1970s. 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 less in its "core". At the same time, the industry was characterised 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, tranquilisers, etc..

### *II.3 The Advent of Science*

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. From the middle seventies on, however, 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 and the biochemical and molecular roots of many diseases. This new knowledge had a profound impact on the process of discovery of new drugs. 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" in that 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, advances which in turn opened up new targets and opportunities for drug therapy.

This improved understanding led to the development of the techniques of "guided search" and of "rational drug design", i.e. to the application of the new biological knowledge to the design of new compounds, as well as to the ways in which they are screened. Researchers are now beginning to be able to "design" compounds that might have particular therapeutic effects.

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 centres of public research and those that were most successful with the older techniques of rational 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 European and Japanese firms appear to have been slow responding to the opportunities afforded by the new science.

This transition 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. 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.

The advent of “biotechnology” had a significant impact on both the organisational competencies required to be a successful player in the pharmaceutical industry through their impact on the competencies required to discover "conventional", small molecular weight drugs and on industry structure in general.

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. 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.

Genentech was quickly followed by a large number of new entrants. Entry rates soared in 1980 and remained at a very high level thereafter, favoured also by the large availability of venture capital and by the gradual establishment of a very favourable climate concerning patenting.

Despite the high rates of entry, it took several years before the biotechnology industry started to have an impact on the pharmaceutical market. The first biotechnology product, human insulin, was approved in 1982, and between 1982 and 1992, 16 biotechnology drugs were approved for the US market. 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).

However, 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.

First, it was 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 hormone) 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 than expected. Second, these companies 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. Thus, they exploited their essential competence and acted primarily as research companies and specialised suppliers of high technology intermediate products, performing contract research for and in collaboration with established pharmaceutical corporations.

Collaboration allowed NBFs to survive and - in some cases - to pave the way for subsequent growth under many respects. First, clearly, it provided the financial resources necessary to fund R&D. Second, it provided the access to organisational 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.

Indeed, large established firms approached the 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. There was enormous variation across firms in the speed with which the new techniques were adopted. The adoption of biotechnology was much less difficult for those firms who had not made the transition from "random" to "guided" drug discovery. For them, 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 organisational 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).

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, in the divisional structure of the company as well. Collaborative research with the NBFs and with universities allowed these companies, in any case, to get access to the new technology and to experiment 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.

Thus, a dense network of collaborative relations emerged, with the start-up firms positioned as upstream 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. Networking was facilitated by the partly "scientific", i.e. abstract and codified nature of the knowledge generated by NBFs (Arora and Gambardella, 1998, Gambardella, 1995), which made it possible, in principle, to separate the innovative process in different vertical stages: the production of new scientific knowledge, the development of this knowledge in applied knowledge, the use of the latter for the production and marketing of new products. In this context, different types of institutions specialised in the stage of the innovative process in which they were relatively more efficient: university in the first stage, the NBFs in the second stage and large firms in the third. A network of collaboration between these actors provided then the necessary coordination of the innovative process. The new firms acted as "middlemen" in the transfer of technology between universities -- which lacked the capability 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 (Orsenigo, 1989).

However, substantial costs remained in transferring knowledge across different organisations, especially for the tacit and specific component of knowledge. Moreover, the innovative process still 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 still require the integration of different disciplines, techniques, search and experimental procedures and routines, which are not generally separable and codified.

Moreover, since knowledge is still fragmented and disperse, and since the rate of technological change is still very high, 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 effects, represents a possible alternative approach to drug discovery and a particular instantiation of the

opportunities offered by the progresses of science (Orsenigo, Pammolli and Riccaboni, 2001). New generations of NBFs have been created which adopt different approaches to the use of biotechnology in the pharmaceutical industry. Large established corporations continue therefore to explore these new developments through collaborative agreements.

The proliferation of NBFs was essentially an American (and partly British) phenomenon. The development of the biotechnology segment in Europe and Japan lagged considerably behind the USA and rested on the activities of large established companies. The British and the Swiss companies moved earlier and more decisively in the direction pioneered by the large US firms in collaborating or acquiring American start-ups. But those firms that had smaller research organisations, that were more local in scope or that were more orientated towards the exploitation of well established research trajectories -- in short, those firms that had not adopted the techniques of "rational" or "guided" drug discovery -- have found the transition more difficult (Henderson and Cockburn, 1994; Gambardella, 1995): almost all of the established French, Italian and Japanese companies -- but also the German giants - have been slow to adopt the tools of biotechnology as an integral part of their drug research efforts.

More generally, ever since the mid-Seventies the American, British and Swiss companies appear to have gained significant competitive advantages vis-a-vis European firms, including the Germans (Gambardella, Orsenigo and Pammolli, 2000). And traditionally the Continental European (except Germany and Switzerland) and Japanese industries have been much less oriented toward innovation than to strategies based on imitation, production and marketing mainly for the domestic market.

### *II.3 Institutional Environments*

The reasons for the differentiated patterns of evolution of the pharmaceutical industry across countries, especially after the advent of the Molecular Biology Revolution are still controversial. There is little question, though, that institutional factors seem to have played a decisive role. Indeed, from its inception, the evolution of the pharmaceutical industry has been tightly linked to the structure of national institutions. The pharmaceutical industry emerged in Switzerland and Germany, in part, because of strong university research and training in the relevant scientific areas. In the U.S. the government's massive wartime investment in the development of penicillin, as we discussed above, profoundly altered the evolution of American industry. In the post-War era, the institutional arrangements surrounding the public support of basic research, intellectual property protection, procedures for product testing and approval, and pricing and reimbursement policies have all strongly influenced both the process of innovation directly and the economic returns (and thus incentives) for undertaking such innovation. We turn to a brief review of these four key areas below.

#### *Public Support for Health Related Research*

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 after the second world war and it is now the second largest item in the federal research budget after defense. Most of this funding is administered through the NIH, although a significant fraction goes to universities. 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 and Dranove, 1995; Cockburn and Henderson, 1996; Maxwell and Eckhardt, 1990).

Public funding of biomedical research also increased dramatically in Europe in the post-war period, although total spending did not even approach American levels.

Jointly with the levels of funding, other factors are likely to have played an important role. In fact, the institutional structure of biomedical research evolved quite differently in Continental Europe as opposed to the USA (and partly to the UK). 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

In Europe, funding has tended instead to be 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, especially in smaller 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.

Moreover, in Continental Europe biomedical research was mainly concentrated in national laboratories rather than in medical schools as happened in the US and the UK. These differences in the levels and sources of funds along with a number of other institutional factors have interacted in Continental Europe to create an environment which in general not only produces less science of generally lower quality but also one in which science is far less integrated with medical practice.

The willingness to exploit the results of academic research commercially also distinguishes the US environment from either Europe or Japan. This willingness has been strengthened since the late 1970s and the passage of the Bayh-Dole Act, and the resulting role of universities as seedbeds of entrepreneurship has probably also been extremely important in the take-off the biotechnology industry.

In contrast links between the academy and industry -- particularly the ability to freely exchange personnel -- appear to have been much weaker in Europe and Japan and it has been argued that the rigidities of the research system of Continental Europe and the large role played in France and Germany by the public, non academic institutions have significantly hindered the development of biotechnology in those countries.

### *Intellectual Property Protection*

Pharmaceuticals has historically been one of the few industries where patents provide solid protection against imitation. However, the scope and efficacy of patent protection has varied significantly across countries.

The U.S and the UK have provided relatively strong patent protection in pharmaceuticals. In contrast, in Japan (until 1976) and in many other European countries including France (until 1963), Germany (until 1968) Italy (until 1978), patent law did not offer protection for pharmaceutical *products*: only *process* technologies could be patented. As a result, in some countries like Japan,

Italy and partly France, firms tended to avoid product R&D and to concentrate instead on finding novel processes for making existing molecules.

The establishment of clearly defined property rights also played a major 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 USA, a tight appropriability regime in the biotechnology industry emerged quite quickly, for example through the Bayh-Dole Act in 1980 and through the granting of very broad claims on patents. In Europe, the scope for broad claims on patents is greatly reduced and usually process rather than product patents are granted. It is often stressed that the lack of adequate patent protection was a major obstacle to the development of the biotechnology industry in Europe. Yet, 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 (Nelson and Merges, 1994)

### *Procedures for Product Approval*

Pharmaceuticals are regulated products. Procedures for approval have a profound impact on both the cost of innovating and on firms' ability to sustain market positions once their products have been approved. As in the case of patents, there are substantial differences in product approval processes across countries.

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 among industrialised countries. Germany but especially France, Japan, and Italy have historically been much less demanding.

In the USA, the 1962 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 and Peltzman, 1974). They certainly led to large increases in the resources necessary to obtain approval of a new drug application (NDA), and they probably caused sharp increases in both R&D costs and in the gestation times for new chemical entities (NCEs), along with large declines in the annual rate of NCE introduction for the industry and 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 an isolating mechanism for innovative rents. Although the process of development and approval increased costs, it significantly increased barriers to imitation, even after patents expired<sup>1</sup>.

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<sup>1</sup> 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

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 the industry. A number of smaller weaker firms exited the market and the proportion of minor local products launched into the British market shrunk significantly. The strongest British firms gradually reoriented their R&D activities towards the development of more ambitious, global products (Thomas, 1994).

In other European countries, procedures for products approval were less stringent. This allowed the survival of smaller firms specialised in the commercialisation of minor domestic products.

### *The Structure of the Health Care System and Systems of Reimbursement*

Perhaps the biggest differences in institutional environments across countries was in the structure of the various health care systems. In the U.S., pharmaceutical companies' rents from product innovation were further protected by the fragmented structure of health care markets and by the consequent low bargaining power of buyers. Moreover unlike most European countries (with the exception of Germany and the Netherlands) and Japan, drug prices in the U.S. are 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), they did not 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 profitability of investments in drug R&D.

Drug prices were also relatively high in other countries that did not have strong government intervention in prices such as Germany and the Netherlands. In the UK, price regulation left companies to set their own prices, but a global profit margin with each firm was negotiated which was designed to assure each of them an appropriate return on capital investment including research, in the UK. The allowed rate of rate return was negotiated directly and was set higher for export oriented firms. In general, this scheme tended to favour both British and foreign R&D intensive companies which operated directly in the UK. Conversely, it tended to penalise 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).

On the contrary, in Japan, France and Italy price regulation was organised in such a way to protect the domestic industry from foreign competition and offered little incentive to ambitious innovative strategies (Thomas 1994, Henderson, Orsenigo and Pisano 1999).

In more recent times, the introduction of cost containment policies in almost all countries has led to profound changes in these systems and in intense debates about the efficiency of alternative systems in resolving the trade-off between lower prices and incentives for innovation (Lacetera and Orsenigo, 2001).

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before a generic version appeared even once a key patent had expired. In 1980, generics held only 2% of the U.S. drug market.

## *Access to Capital*

A further factor which is often cited as a key variable in explaining the divergent development of biotechnology in the USA vis-a-vis Europe and Japan is the availability of venture capital. It is commonly believed that lack of venture capital restricted the start-up activity of biotechnology firms outside the U.S. Clearly, venture capital -- which is to some extent a largely American institution -- played an enormous role in fueling the growth of the new biotechnology based firms, (or "NBFs"). However, at least in Europe, there appear to have been 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 U.S. biotechnology firms, collaborations between the new firms and the larger, more established firms provided a potentially even more important source of capital.

## **III. The Model**

### *III. 1 Challenges for a history-friendly model*

As it was discussed in the Introduction, there are several important conceptual issues that are raised by an analysis of the evolution of the pharmaceutical industry. In particular, we mentioned three of them: the relationships between the properties of the regimes of search, the nature of markets, the patterns of competition and the evolution of market structure; the relationships between science and innovation; the role and the impact of alternative forms of public policy and regulation.

In this preliminary version of the paper, we shall address only a subset of these issues. In particular, we do not engage here in the analysis of public policies, regulation and intellectual property rights. Moreover, we start from a set of "heroic" simplifying assumptions. The aim of this first step of our analysis is less to develop a model capable of replicating in detail the actual – albeit stylised – history than to:

- i) check the extent to which an extremely simplified - but largely accepted - representation of the process of drug discovery and development, namely what has been called the "lottery model" (Sutton, 1999) – captures the essence of the patterns of industrial evolution in pharmaceuticals in the age of random screening;
- ii) begin to examine the changes in the search procedures and market structure following the advent of molecular biology.

The thrust of the story can be summarised as follows. A number of firms competes to discover, develop and market new drugs for a large variety of diseases. They face a large space of – at the beginning - unexplored opportunities. However, the search for new promising compounds is essentially random, because the knowledge of why a certain molecule can "cure" a particular disease and of where that particular molecule can be found is limited. That is to say, the role of "science" here is modest. Thus, firms explore randomly the "space of molecules" until they find one which might become a useful drug and patent it. The patent provides protection from imitation for a certain amount of time and over a given range of "similar" molecules. After discovery, firms engage in the development of the drug, without knowing how difficult, time consuming and costly the process will be and what the quality of the new drug will be. Then, the drug is sold on the market, whose notional size is defined by the number of potential patients and by its "natural" rate

of growth. Marketing expenditures allow firms to increase the number of patients they can access. At the beginning, the new drug is the only product available on that particular therapeutic class. But other firms can discover competing drugs or imitate. Indeed, firms are characterised by different propensities towards innovation on the one hand and imitation and marketing on the other. The innovator will therefore experience a burst of growth following the introduction of the new drug, but later on its revenues and market shares will be eroded away by competitors and imitators.

The discovery of a drug in a particular therapeutic class does not entail any advantage in the discovery of another drug in a different class (market) – except for the volume of profits they can reinvest in search and development. Moreover, the various sub-markets (therapeutic categories) that define the overall pharmaceutical industry are independent from one another also on the demand side: an anti-ulcer drug is useless for a patient suffering Alzheimer. As a consequence, diversification into different therapeutic categories is also purely random. Hence, firms will start searching randomly again for a new product everywhere in the space of molecules. Firms' growth will then depend on the number of drugs they have discovered (i.e. in diversification into different therapeutic categories), on the size and the growth of the markets they are present in, on the number of competitors, on the relative quality and price of their drug vis-a-vis competitors. In few cases, a firm can discover a blockbuster, i.e. a high quality drug that has a large and fast growing market. Given the large number of therapeutic categories and the absence of any form of cumulativeness in the search and development process, no firm can hope to be able to win a large market share in the market, but – if anything – only in specific therapeutic categories for a limited period of time. As a result, the degree of concentration in the whole market for pharmaceuticals and in any individual therapeutic category will be low. However, a few firms will grow and become large, thanks essentially to the discovery of a “blockbuster” and to diversification. Under these conditions (absence of significant economies of scale and scope, independence across sub-markets), the pattern of firms' growth is likely to resemble a simple Gibrat process, generating a skewed distribution of firms' size.

The advent of “science” (i.e. molecular biology) starts to change this picture. In the model, we try to introduce a first, very rough, reduced form of the cognitive processes underlying drug discovery after the molecular biology revolution. To a large extent, our attempt is inspired by the so-called Arrow-Nelson model about the effects of scientific research on the productivity of industrial research. However, we introduce some modifications to this approach, aimed at capturing the simple idea that science does not simply simplify the search space, but it deforms it and generates an explosion of alternative hypotheses to be tested (Orsenigo, Pammolli and Riccaboni, 2001).

In our model, scientific knowledge begins to shed light upon the mechanism of action of some drugs and the biochemical and molecular roots of some diseases. This improved understanding allows firms to try to “design” compounds that might have particular therapeutic effects and to focus search into particular directions. Moreover, science makes new products potentially available and improves the “quality” of some drugs.

On these bases, new science-based firms enter the market, trying to discover new drugs. Yet, science does not simply provide (imperfect) information on the properties of the search space. There might be multiple competing trajectories for eventually discovering a new drug and many of them will prove to be dead-ends. The new firms are specialised in specific techniques and applications and cannot change their trajectories and easily apply their specific competencies to different areas. However, they have very little funding and – even when they succeed in discovering a new drug – they don't control the resources to developing and marketing it.

Thus, only few of the new biotechnology firms (NBFs) will succeed in discovering, developing and selling a new drug. Conversely, extant big pharmaceutical companies do not react immediately to the new opportunities and when they eventually adopt the new technologies they have to gradually “learn” the new knowledge base. However, they have plenty of financial and marketing resources. Moreover, they are able – in principle - to “screen” wider subsets of the search space: they are “generalists” rather than “specialists”<sup>2</sup>. Against this background, big pharmaceutical companies and NBFs may find it profitable to strike collaborative agreements, whereby NBFs complete some specific project with additional funding provided by their large partners. The drug is then developed and (if successful) marketed by the big pharma corporation, paying a royalty to the NBF. As a consequence, a network of alliances begins to emerge.

### *III. 2. The model*

In this section we describe the basic structure of the model.

#### *III.2.1 The topography*

The technological and market environment in which pharmaceutical firms are active is composed by several therapeutic categories (TC).

Each **therapeutic category** (TC) has a different economic size according to the number of potential customers. This economic size is expressed by total potential sales of each TC ( $V$ ). It is exogenously given in the model and it is known by the firms. In our model there are  $n$  therapeutic categories, TC, each with a specific  $V$ .  $V$  is set at the beginning of each simulation and is a random number drawn from a normal distribution.  $V$  grows at a certain rate, ranging between 0 and 2% in the first part (half of the total period) of the simulation, and between 0 and 4% afterwards, when biotechnology is introduced. Firms active in a certain TC get a share of  $V$  equal to their market share.

Within each TC there are a certain number of **molecules**  $M$  (in our simulations, 150), which firms aim to discover and which are at the base of pharmaceutical products that later on are introduced in the market. Each molecule  $M$  has a certain quality  $Q$ .  $Q$  is expressed in terms of “height” of a certain molecule and it is set randomly. In most of the cases, it is equal to zero; in few cases, it has a positive value drawn from a normal distribution.

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<sup>2</sup> In this version of the model, we do not yet consider the potential economies of scope made possible by the new biological knowledge. Nor do we introduce the notion that in order to discover a new drug, different complementary fragments of knowledge have to be found and combined together. Both are indeed crucial aspects of the search regime prevailing now in pharmaceuticals, which bear fundamental implications for market structure. The analysis of these phenomena will be the subject of future work.

Figure 1 depicts the “landscape” in term of therapeutic categories and molecules that firms face.

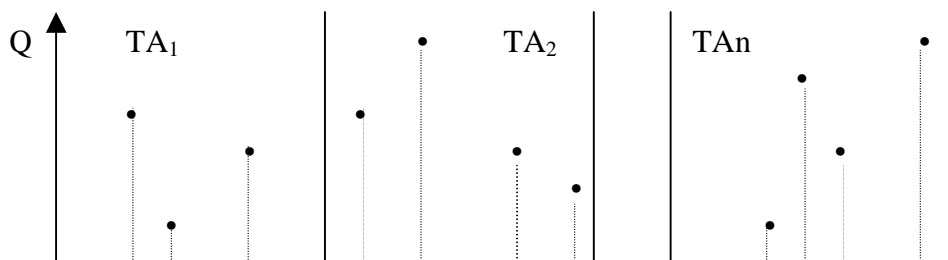


Figure 1: Therapeutic categories and molecules

A **patent** has a specific duration and width (extension). Once a patent expires, the molecule becomes free for all the firms. A patent gives the firm also the right to extend the protection on the molecules situated in the “neighborhood” of the molecule that has been patented. Thus, competing firms are blocked in the development of potential molecules near the patented one.

Once the patent has been granted, the firm can start the **development** of the product based on that molecule. The value of the product  $PQ$  is a function of the value of the molecule  $Q_i$ . That is:

$$(1) \quad PQ_i = Q_i \pm \alpha * Q_i, \quad i=1, 2 \dots 150 \text{ for each TC}$$

where  $\alpha$  is a random variable. In the simulation the value of  $\alpha$  is randomly drawn from a uniform distribution ranging from  $-0.25$  to  $+0.25$ .

Each product gives a certain level of utility to consumers (see section 3 for a discussion of demand)

### III.2.2 The firms

#### III.2.2.1 The basic features of firms

The industry is populated by firms, endowed with a budget,  $B$ , which initially is equal for all firms. At period 1, only half of the firms start their activities, and are labeled as “Incumbents”. The other half, “NBFs”, will start operating later, when the “biotechnology revolution” occurs.

Coherently with an evolutionary approach, firms have a very limited understanding of the environment in which they act and behave following simple rules of thumb or routines. Specifically, firms are characterised by three activities -*search, research and marketing*- but with different intensity in these activities. Some firms in fact may want to spend relatively more on search and research and less on marketing; other firms do the contrary. In the model, the marketing propensity by firms,  $\mu$ , is defined by a share of the budget randomly set in the interval  $[0.2-0.8]$ . Relatedly the research propensity by firms is defined by a share of the budget that complements the share of the propensity to marketing. That is  $1 - \mu$ .

Firms’ budget  $Bud$  is divided for search, research and marketing activities according to the specific propensities discussed above:

Resources for search and research ( $B_s$ ):  $[1-\mu]B$   
 Resources for marketing ( $B_a$ ):  $\mu B$

Firms' profits will be divided accordingly.

### ***III.2.2.2. Innovators and imitators***

Firms can be *innovators or imitators*. The propensity to research determines whether a firm is an innovator or an imitator. If a firm has a propensity to research  $[1-\mu] > w$  (a random number drawn from a uniform distribution ranging from 0 to 1 in each period), then the firm is an innovator. If the firm has a propensity to research  $[1-\mu] < w$ , then it will be an imitator. While the propensity to research is given initially and does not change over time,  $w$  does: as a consequence, firms with a very low propensity to research will be most of the times imitators, and the opposite will hold for firms which will be most of the times innovators. A lot of firms however will be imitators in certain periods and innovators in other periods.

#### *a. Imitative activities*

If a firm follows an imitation strategy, it looks for an already discovered molecule, whose patent has expired. Imitators rate molecules according to their quality  $Q$ . The probability of choosing a molecule is proportional to  $R$ , which is a function of  $Q$ :

$$(2) \quad R = Q \pm \beta Q,$$

where  $\beta$  is a random variable. In the simulation the value of  $\beta$  is drawn from a uniform distribution ranging from  $-.25$  to  $+.25$ .

“Incumbent” firms will be able to choose an imitation strategy both before and after the emergence of biotechnology. By contrast, “NBF” will always choose innovative strategies. Let us concentrate on innovative activities.

#### *b. Innovative activities*

Innovative activities take place both during the random screening period and in the science guided search.

If a firm is an innovator, it looks for new molecules and spends in Search. The method of search will differ before and after the emergence of biotechnology. We will thus distinguish between “random screening” and “science-guided” search eras. Before this, we recall that a major simplifying assumption that we use in this paper is that firms can take only one project at a time. In other words, they do not carry out parallel R&D projects, but diversification is sequential. This holds in both methods of search.

- *Random screening*

Firms pay an amount of money,  $S$ , in search, which is given by:

$$(3) \quad S = \sigma B_s$$

where  $\sigma$  is invariant and firm specific. It is randomly drawn from a uniform distribution between 0.05 and 0.15.

### *Patented molecules*

According to the level of its budget  $B$ , a firm extracts a certain number of TCs. In each TC, the firm extracts a molecule. Firms do not know the “height”  $Q$  of a molecule: they only know whether  $Q$  is greater than zero or not. If the molecule has a non-zero value  $Q$  and has not been patented by others, then a patent is obtained. If the firm experiences successful extractions in more than one TC and finds more than one positive  $Q$ , the firm starts research activities on the patented molecule of the TC that has the highest value  $V$ . The molecules that are not selected become part of the next round search process. The values of the market of the TCs to which the current molecules belong are compared with the values of the markets of the TCs with positive  $Q$  extracted in the next round: the TA of the highest value is selected.

According to this mechanism, two effects are present. First, innovators will progressively increase their probability of finding molecules that belong to high value TCs, since they can rely on their protected “sleeping molecules” in addition to those extracted at the beginning of each project. Second, after a certain number of rounds of search, the TCs with the highest values become relatively congested.

If the search is successful, the firm moves to Research (see 2.4). Only when research activities are over (i.e. after a patent has been obtained), the firm will start another search.

- ***Science guided search***

At time  $T (=90)$  the biotechnology era starts and the new “NBFs” enter the market. NBFs start doing research according to a new method. “Incumbent” firms will shift to such new method later on. The ones with a higher propensity to search (that is, with a lower  $\mu$ ) start first.

Firms choose the TC on which they do their search according to the same “draw scheme” we have described above (except for the consideration of “sleeping” TCs). Moreover, we assume that the new scientific paradigm would have more profitable application in certain markets. Therefore, we suppose that, at  $T=90$ , some TC will “jump” to a higher value  $V$  (recall that, moreover, such value increases, over time, at a certain rate).

Once a TC has been selected, each firm focuses on a “subsample” of molecules within it. The width of such interval is firm specific and time invariant, and is randomly drawn from a uniform distribution between 20 and 40. Within this interval, the firms are able to “see” the “height”  $Q$  of each molecule, and will try to reach the one with the highest  $Q$ .

However:

- firms are not able to see the “real” quality of each molecule. The  $Q$  they perceive is distorted by the distance from the point in which firms are (firms are “myopic”), but, if they do research on a given interval for more periods, such “experience” improves the perception, that is, reduces the distortion. Moreover, the larger the interval is, the higher, “coeteris paribus”, the distortion. This last assumption introduces a trade-off between the width of the search sample, which

increases the probability to find a “good” molecule, and the myopia such width might generate;

- if the molecule perceived as the best one is “too far” from the point where a firm start its research, it is not possible to reach it with only one “step”. So firms continue their research in the next period.

An implication of these two assumptions is that the molecule “perceived” as the best can change during the research process.

If the search is successful, the firm moves to the development of the product. Only when research activities are over (i.e. after a patent has been obtained), the firm will start another search.

### *III.2.2.3 Agreements*

At each step of its “biotech” search, an Incumbent firm may decide to strike an agreement with a NBF. In this version of the model, we define the following process. If an incumbent firm has a propensity to search lower than a given value (in our exercises, 0.6, that is,  $\mu > 0.4$ ), it controls whether any NBF is doing research in the same TC, and looks for a NBF which is “closer” to the molecule that the Incumbent perceives as the “best” one. If so, it pays a share of its budget to this NBF and stops doing research. The NBF will keep on its research pattern (as described above), but, when it reaches a molecule, the “incumbent” partner will develop it and “own” the product, but will share the revenues of its commercialisation with the NBF partner.

### *III.2.2.4 Research Activities*

By “research activities” we mean the development of the product. If the molecule is potentially interesting in the random screening period (i.e., it has a height greater than zero), or if it has the highest perceived quality in the biotech phase, the firm starts a project, using the budget  $B_s$  (once  $S$  has been paid). Both innovators and imitators do research. In each period, the progress that a firm makes towards  $Q$  in each period (STEP) is randomly drawn, and ranges from 1 to 6 in the first part of the simulation, and from 1 to 10 in the biotech phase. Firms that move ahead faster in their research per period, pay more for each unitary step (the unitary cost  $C_r$  of each step increases as BTR increases), according to the following relationships:

$$(4) \quad C_r = (C_{ur} * \sum_i^{STEP} i) / STEP$$

where  $C_{ur}$  is the cost of a single step for a firm that has a BTR equal to 1 (i.e. it progresses with 1 step each period).  $C_r$  for imitative firms is set  $\frac{1}{4}$  of the  $C_r$  of innovating firms.  $C_r$  is about 1% of the budget.

With its resources ( $B_r$ ), a firm may be able to reach  $Q$  at the end of his research process. In this case it starts the development and commercialisation of the product. Otherwise, if  $Q$  is too “high” for the resources  $B_r$  of the firm, the project fails.

Moreover, a product must have a minimum quality to be allowed to be sold in the marketplace. In other words, products are subject to a “quality check” by an external agency (e.g. the FDA). In this

version of the model the quality check is simply defined as a minimum quality,  $Q$ , that the product must have. Below this value (a parameter of the model), the drug cannot be commercialized and the project fails.

If the product is obtained from a new molecule, it is labeled innovative product. If it is obtained from a molecule whose patent has expired, it is labeled imitative product.

#### III.2.2.4 Marketing activities

As previously mentioned, if a firm reaches  $Q$ , it has to start to develop it and then launch it on the market. The firm has  $B_a$  available for that purpose.  $B_a$  is divided by the firm in two parts, with shares  $x$  and  $1-x$  (equal for all firms).

$B_a * x$  defines the marketing investment  $A_j$  for the product  $j$ . It is spent once, at the moment of the launch of the product. This amount of marketing will be eroded with time ( $eA$ ). In addition, the firm will profit from a marketing spillover from its previous products  $k \neq j$ . Therefore

$$(5) \quad A_{jt} = A_j * (1 - eA) + \text{spillover } \Sigma A_k$$

$B_a * (1-x)$  defines the total yearly marketing expenditures. Yearly marketing expenditures  $AM$  will therefore be:

$$(6) \quad AM = (1-x) * B_a / T$$

In the simulations,  $x$  is equal to 0.5, erosion ( $eA$ ) = 0.01 and  $T=20$ .

#### III.2.3 Utility, demand and market share

Drugs are bought on the marketplace by groups of heterogeneous consumers. In this version of the model we do not distinguish between patients and physicians. Decisions to buy a specific drug depend on several factors, which together yield a specific “merit” to each drug. product  $j$ . The value of this “merit”,  $U_j$ , is given by:

$$(7) \quad U_j = QP_j^{\alpha} * (1/m)^{\beta} * A_j^{\gamma} * AM_j^{\delta}$$

$QP_j$  is the value of the product quality.

$m$  is the desired rate of return that each firm wants to obtain from its drug. In the model, thus, we do not explicitly model pricing decisions. We simply assume that firms will charge a price that is expected to yield the desired rate of return over a certain period. Other things being equal, the higher the desired rate of return, the higher will be the price and the lower will be the demand. In order to avoid making specific (and rather arbitrary) hypotheses on the details of the pricing decision of firms, we simply assume that demand is inversely related to the desired rate of return.

$A_j$  is the marketing investment for that product and  $AM_j$  is the yearly marketing expenditure for the product  $j$ . Exponents  $\alpha$ ,  $\beta$  and  $\gamma$  are TC specific.

In our simulations,  $m$  is equal to 0.2 for innovative products and 0.1 for imitative products.  $\alpha$  is set equal to 1,  $\beta$  equal to 1,  $c$  equal to 0.2 and  $d$  equal to 0.1. For all of these parameters, we added a random component.

The market share  $MS_{ij}$  of the firm  $i$  for the product  $j$  in each TC is then proportional to its relative merit as compared to other competing drugs in the same TC and it is given by:

$$(8) \quad MS_{ij} = U_{ij} / \sum U_{TC}$$

Firms may have more than one product in a TC. Thus their market share in a TC is the sum of the market shares for all its products. Because  $QP_j$  and  $A_j$  are defined at the moment a patent is obtained and  $m$  is given and equal for all the innovative or imitative firms, firms have a rather constant market share  $MS$  until a new  $M$  is patented.

### III.2.4 Budget and Accounting

Revenues of firm  $i$  for product  $j$  are:

$$(9) \quad \pi_{ij} = MS_{ij} * V_{TA}$$

Because firm  $i$  may have more than one product, total revenues are the sum of revenues obtained from all the products that firms have:

$$(10) \quad \pi_{itot} = \sum_j \pi_{ij}$$

## IV. The simulation runs: the random screening period and the molecular biology revolution

### IV.1 The random screening period; the dynamics of market structure and innovation

As discussed previously in Section 3, in our simulations there are 100 TCs, with their value  $V$  growing at a certain rate, ranging between 0 and 2% in the random screening period (half of the total period) of the simulation.. Within each TC there are a certain number of molecules  $M$  (in our simulations, 150),

In the early days of the pharmaceutical industry, 40 firms with the same budget start their innovative and imitative activities. They differ in their propensity to research and marketing, and in their rate of progress. In the random screening period, the dynamics of innovation and market structure in this industry is the following. Innovative firms start doing their innovative activities by searching over the therapeutic categories. Some of them will succeed to find a molecule with  $Q > 0$ , patent it and start doing their research according to the process described in the previous pages. Once research is completed, they start doing their marketing activities. Market demand for the product will go to those firms that have a higher product quality, higher initial marketing investments and higher marketing yearly expenditures. Firms with larger demand will obtain higher

market shares and higher revenues. Once the patent expires, the molecule becomes available on the market. Imitators do not have to do any search for new molecules. Rather they look around among existing available molecules whose patents have expired. They rate the molecules that they find according to their level of Q and choose the highest. Then they start doing their research on that molecule, and they proceed as in the case of innovators (with the exception that now, once their research is over, they do not obtain a patent). Then they start doing their marketing activities.

Our definition of innovative and imitative firms is an ex-post one, and depends on the amount of innovative vs. imitative products that they have. Most firms in fact have both innovative and imitative products. Thus it is possible that a firm may change its innovative or imitative status over time.

In a previous paper (Malerba-Orsenigo,2001) we have examined the long term evolution of the pharmaceutical industry in the random screening era (i.e. period and before the biotechnology revolution). Results show that in each therapeutic category concentration (in terms of the Herfindahl index) after an initial upsurge tends to decrease quickly. Similarly, the overall market concentration is high at the beginning, and then drastically declines as more firms discover more molecules in various therapeutic areas, although it is always lower than concentration in individual therapeutic categories. Selection is intense and part of the initial set of firms exit the market. In each therapeutic category there are an increasing number of firms (at the beginning only innovators, and then also imitators) and of products. However, a skewed distribution of firms' size emerges, with a few large firms (mainly innovators, who are present in a high number of TCs), and many smaller companies (mainly imitators). Standard tests of the Gibrat Law on the growth of firms are not rejected. The overall market share of innovative firms is high. On average each firm is increasingly present in more than one therapeutic category. In the long run, almost all the therapeutic categories are discovered. The performance index for the industry as a whole, indicating the share of total potential quality actually reached by firms in the industry, however, is around 35%. The microdynamics differs across therapeutic categories: in a few TCs there are no firms, while in the others several firms are present. In most TCs the Herfindahl index is always rather similar. In each TC the number of products may range from zero to tens. The relationship between innovative and imitative products is such that on average to an innovative product corresponds an imitative product. In sum, the model does a relatively good job in replicating – at a rather generic and qualitative level - some of the fundamental properties of the patterns of competition and evolution of the random screening period, especially as concentration, the patterns of firms' growth and size distribution, the relationship between innovators and imitators and high levels of profitability are concerned.

This is what our “random screening period” part of the model (period 1 to 90) shows for averages of 50 simulations. Tables 1, 2, 3, and 4 show the overall Herfindahl index of the total market, concentration in each therapeutic category, and alive firms, up to period 90.

In that previous paper (Malerba-Orsenigo,2001) we have also explored also some alternative runs examining the role of demand and technological opportunities, different patent protection and increase in costs and changes in regulatory regimes (tables are not reported here). We have found that in situations of *no demand growth* (i.e. if the value of each TA would have been constant over time) results show that concentration in each TA, the share of innovative firms, the overall total quality (the performance index) and profitability would be much lower than in the standard case. This means that no growth in demand would erode the revenues and the market share of innovators and would benefit imitators. On the contrary demand increases benefit innovators by giving them greater revenues, higher profitability and higher growth.

Would an increase of technological opportunities have countervailed the effects of no demand growth? Results show that *greater technological opportunities* do increase the share of innovative firms, the number of TCs reached, the overall quality and profitability, but do not increase concentration. In fact, higher innovative opportunities increase both innovation and competition among innovative firms. These results indicate that both the growth in demand and the increase in technological opportunities favour innovators and increase the amount of product quality. However, while demand growth increases concentration, an increase in technological opportunity does not.

We began also to explore the consequences of *an extension of patent duration*. As expected, an increased patent protection lowers the number of surviving firms and increases the share of innovative firms and the average level of concentration in each therapeutic category, but not overall concentration. However the number of TCs discovered decreases and the total quality remains practically unchanged (if anything, it decreases somewhat). In other words, stronger patent protection implies less exploration and less diversification for each firm. Finally, it is worth noting that, other things being equal, the effects of increased patent duration tend to have diminishing returns. Above certain minimum levels of protection, further increases have no effects at all.

Then we explored *an increase in the cost of research* taking place from a certain period on and increasing constantly over time. Simulation results show that in this case selection is stronger, the number of firms is reduced, with a much higher level of concentration in individual TCs (but not on the whole) and a higher market share of innovative firms (but a lower number of TCs discovered). From this perspective, an increase in costs has effects similar to the one of stronger patent protection. However, differently from this latter case, higher costs imply also a lower performance index. Finally, *an increase in the stringency of approval procedures* with the increase in the quality check for obtaining a patent, has no effect on the level of concentration or the overall market share of innovative firms, but a drastic reduction in the number of TCs discovered and a lower performance index.

This was basically our exploration of the random screening period.

#### *IV.2 The biotechnology revolution: NBF and the division of labour with the incumbents*

The biotechnology revolution takes place at period 90 and introduces science guided search. (see the discussion of section 3). As a consequence, some TCs will have their Vs grow at higher rates (between 0 and 4%). At the moment of discontinuity, 40 NBFs enter the industry. With the new techniques, they are initially better in search than the incumbents. However after a while also incumbents shift to biotechnology.

The dynamic of competition between incumbents and NBFs is discussed by considering two cases:

- a) The first one in which Incumbents and NBFs do not make any agreement (No Agree case in the Tables). In this case, for their survival, NBF have to discover a product.
- b) The second one in which Incumbents and NBFs n make agreements along the lines discussed in Section 3 (Agree case in the Table). In this case, for their survival NBF have either to discover a product or strike an agreement with an incumbent.

From our simulations (averages over 50 periods) it emerges clearly that from a traditional point of view related to simple measures of market concentration, the biotechnology revolution does not make that much difference. In fact the overall level of concentration (which is already rather low at

period 90) does not fall to even lower levels as a consequence of the entry of the new NBF. (see Table 1). We also compared the dynamics of concentration to a situation where the biotechnology revolution does not occur (see Run Pharma): also in this case, biotechnology does not decrease concentration levels even if 40 new firms enter the market. Also when concentration in each TC is examined (Table 2), with biotechnology concentration continues to decrease in the same way as in the case of no biotech revolution (see Run Pharma). So, in terms of market structure, there is a considerable increase in the heterogeneity of actors (incumbents and NBF), but no significant change in the concentration. This is due to the fact that NBFs remain always of a rather small size.

// TABLES 1 AND 2 ABOUT HERE//

The dynamics in the number of firms when no agreements are possible is illustrated by Tables 3 and 4. The number of incumbents decreases initially (before the biotechnology revolution) and then remains stable afterwards. On the contrary, the entry of NBFs with the biotechnology revolution is then soon followed by a selection process, in which several NBF, which do not find a product, have to exit the market.

// TABLES 3 AND 4 ABOUT HERE//

The situation is different if NBFs can strike agreements with incumbents. In general, the number of surviving NBFs does not change much. However, a larger number of NBFs can survive in the marketplace without producing drugs and obtaining funds from Incumbents (Tables 5 and 6)

// TABLES 5 AND 6 ABOUT HERE//

What are the benefits of the biotechnology revolution for the incumbents and for NBFs which follow an agreement strategy ? Incumbents definitively benefit from the biotechnology revolution, because they increase their size with respect to a no-biotech scenario (see Run: Pharma). The benefit is even higher when incumbents may strike agreements with the NBF (Table 7). Also NBFs benefit from the possibility of agreements, because they receive funding from incumbents even if they do not discover any new product. Thus, the growth of the NBFs is much larger and much smoother as compared to the case without agreements (Table 8).

// TABLES 7 AND 8 ABOUT HERE//

Interestingly enough, with biotech the number of innovative products decreases (Table 9). This is because in the pharmaceutical case without biotechnology, companies choose all the products that have quality greater than 1, while in the biotechnology regime firms are more selective in their choice and they take more time to reach innovative products. However, as expected, the average quality of innovative products (Table 10) is higher for biotechnology products compared to a situation in which the biotechnology revolution would not have occurred. In particular, the introduction of biotechnology generates a sharp drastic increase in the quality of the innovative products of around 3-4%.

// TABLES 9 AND 10 ABOUT HERE//

Similarly, in the era of biotechnology the average number of therapeutic categories where firms are present tends to decrease, since smaller firms – the NBFs - enter the market and have less opportunities to diversify into different TCs (Table 11).

// TABLE 11 ABOUT HERE//

What about the dynamics of the NBF firms? Here one could identify two types of NBF. A smaller group is composed by the NBFs which have found a product by their own and in the same time are in an agreement with an incumbent for the search of a new product. They are the more articulated NBF in terms of strategies (in-house development plus agreement). The majority of NBF however follows just a strategy of signing agreements with some incumbent. As Tables 12 and 13 show, the number of agreements is steadily increasing (up to 22), but the number of products jointly developed through agreements remains rather low (up to 4) (Table 14). This means that an agreement is successful approximately 1 out of 8 times. In any case, even in case of failure, the NBF has received enough funding from the big incumbent and has now the resources to continue to search in other directions. However, also the incumbent has an incentive to strike an agreement with the small NBF, because the NBF does what the incumbent would have done in the search for a new molecule.

// TABLES 12, 13 AND 14 ABOUT HERE//

In sum, our simulation results show that in the molecular biology period behind the same low overall concentration level (present also in the random screening period) we have a quite different market structure in terms of higher heterogeneity of firms and types of actors and we see a greater division of innovative labour, with the incumbents and the NBFs profiting from complementary capabilities through the possibility of striking collaborative agreements for obtaining new products.

## V. Conclusions

This is a first attempt to model the long term dynamics of market structure and innovation in the pharmaceutical industry in a history friendly way. We have tried to answer some key questions related to the relationships between the nature of the search space, the patterns of competition and industry evolution in the age of random screening and in the age of molecular biology.

We consider the results encouraging. The model is actually able to replicate some of the key features of the pharmaceutical industry in these periods. Other results are not entirely history-friendly and deserve further scrutiny. Our results show indeed that in the standard simulation there is a moderate concentration in each TC, but a rather low level of concentration in the overall market, while innovative firms continue to maintain a key role. We have also shown that both demand growth and increase in technological opportunities have similar effects on the role of innovative firms, exploration and total quality, but a contrasting effects on concentration (positive for demand growth, and less so for technological opportunities). We have also explored different situations of patent protection. As expected, an increase in patent protection increase concentration but decreases exploration, while the opposite holds for no patent protection. Interestingly enough, an increase in patent protection is not able to countervail the negative effects of no growth in demand as far as quality and exploratory activities are concerned. Finally, an increase in the cost of research or in the stringency of approval procedures have quite different effects on concentration,

exploration and quality: the first increases concentration and reduces quality, the second does not affect concentration, but affects negatively exploration as well as quality.

The analysis of the transition to science guided search produces also some interesting results. Concentration does not change, despite a significant entry of new firms. The number of innovative products decreases but their average quality improves significantly. A dense network of agreements between incumbents and NBFs start to develop. Collaborative relations allow for the survival of many NBFs and for the further growth of some Incumbents, that benefit from collaboration for discovering better drugs.

This is only the first step. First, we shall have to consider the role of some variables that have been consciously excluded by our model so far, but that might have an important role in explaining the dynamics of pharmaceuticals even in the era of random screening. First of all, economies of scale and scope. Second, our model does not consider adequately the effects of exogenous advances in science and technology. Third, we need a much more structured analysis of the demand side and of the effects of alternative policy regimes in terms of pricing, patenting, product approval regulations and finally price controls.

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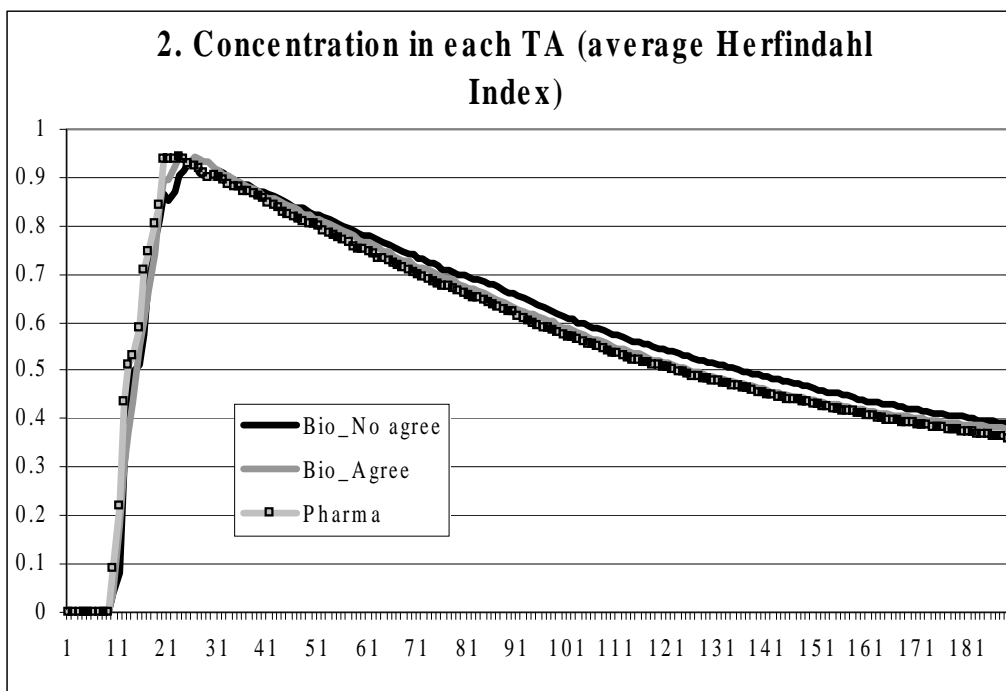
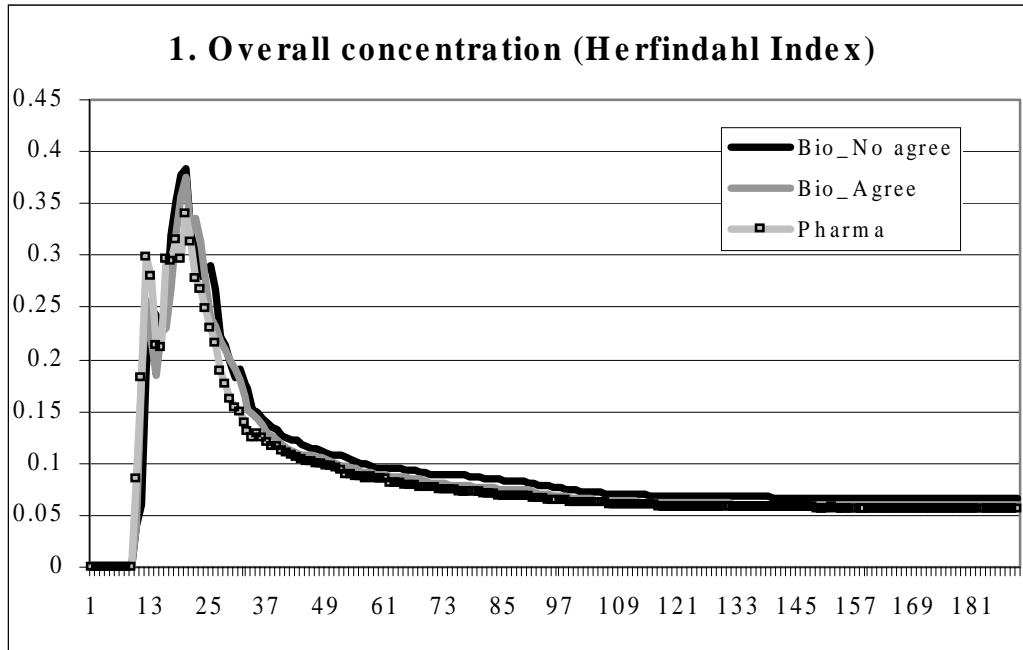
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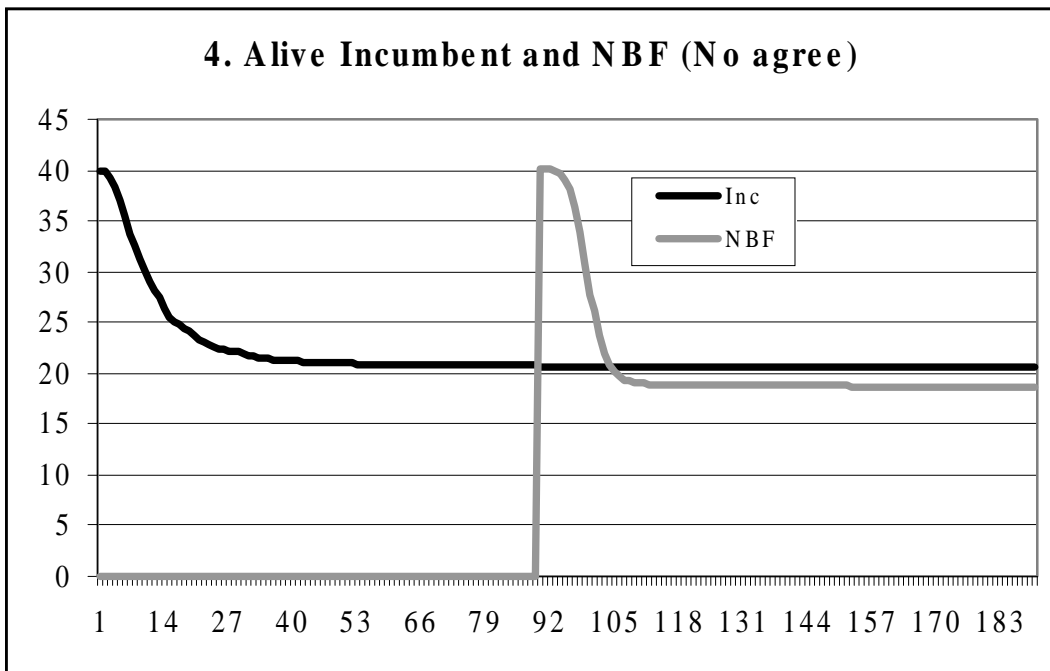
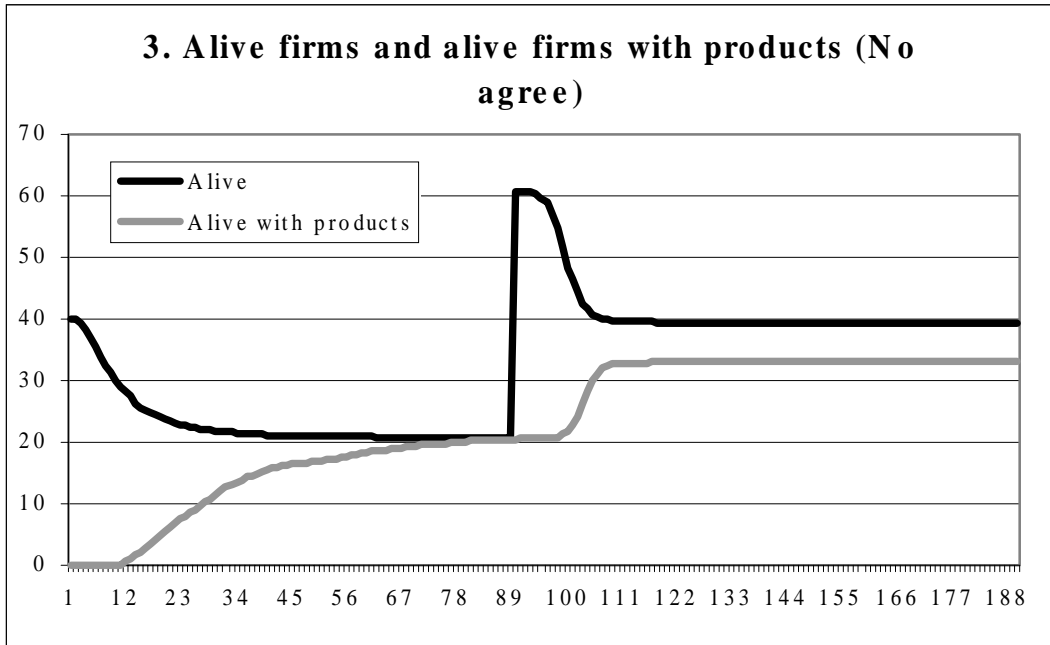
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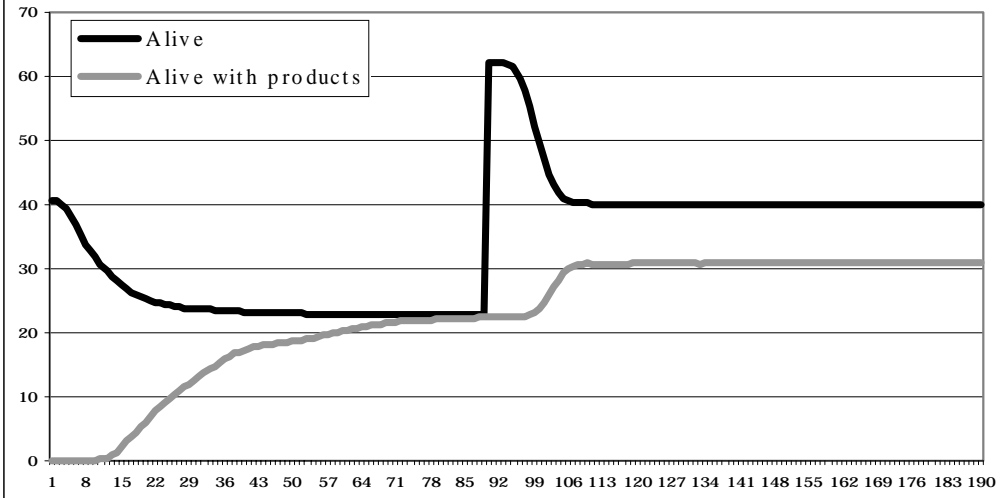
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# TABLES

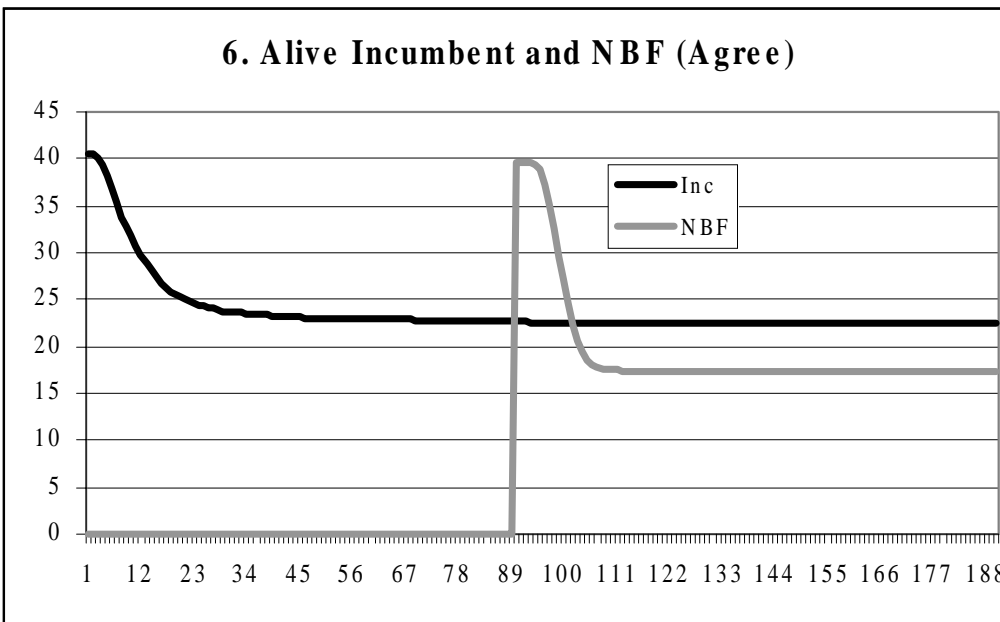




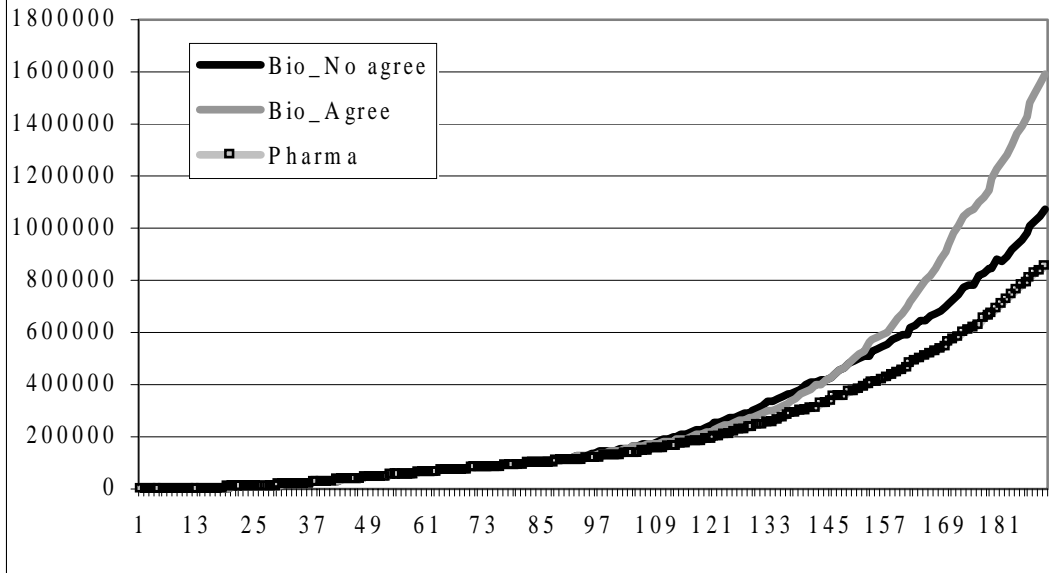
### 5. Alive firms and alive firms with products (Agree)



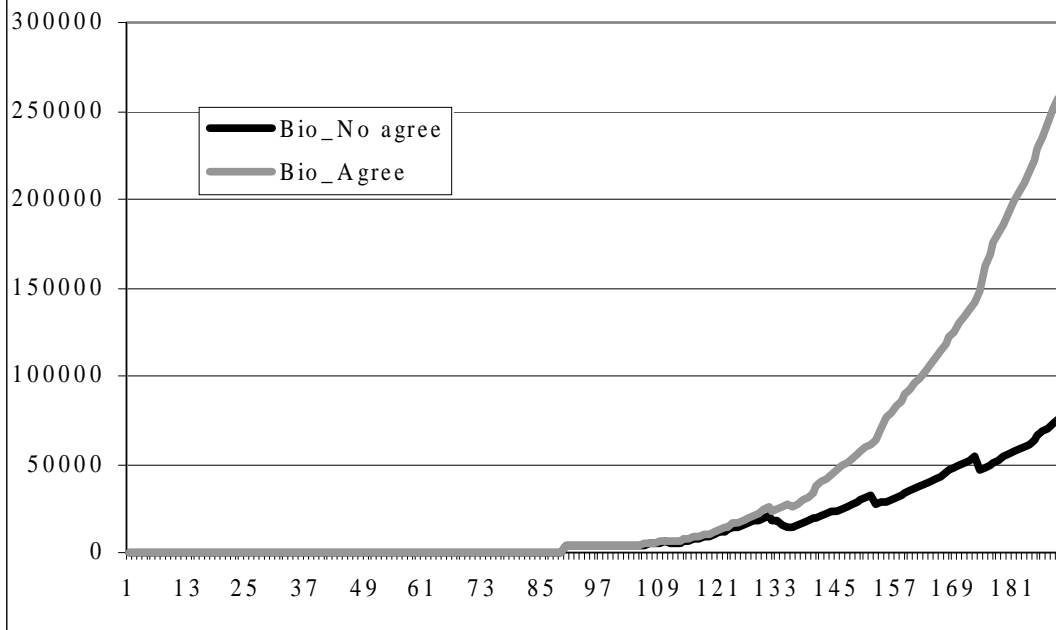
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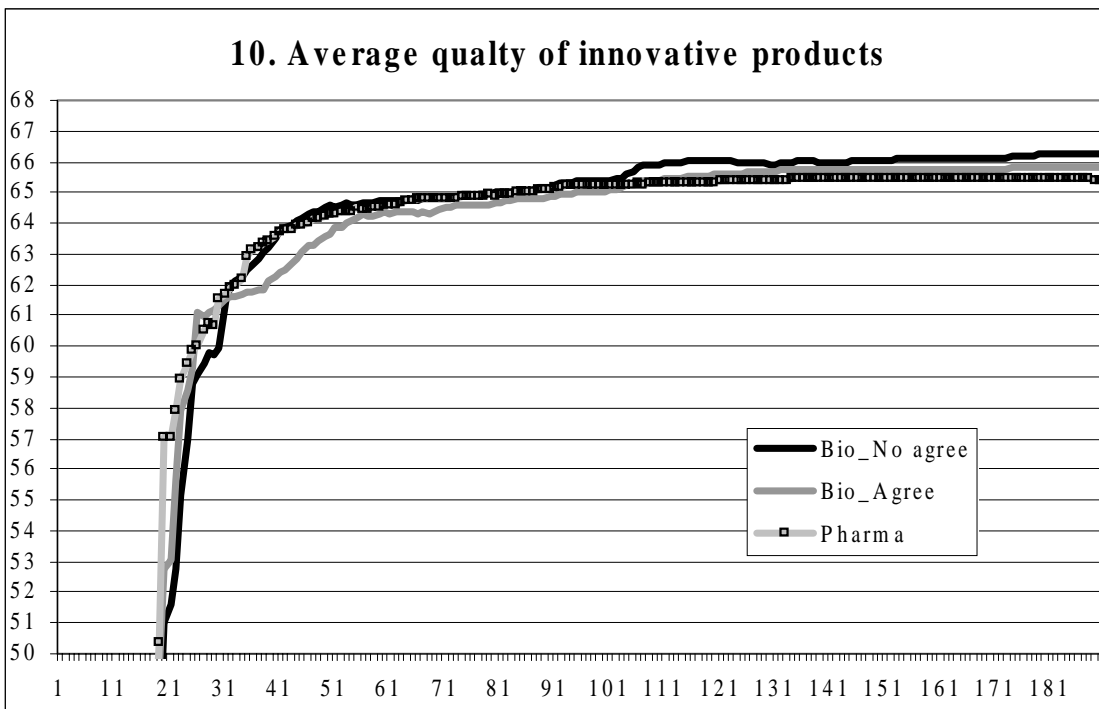
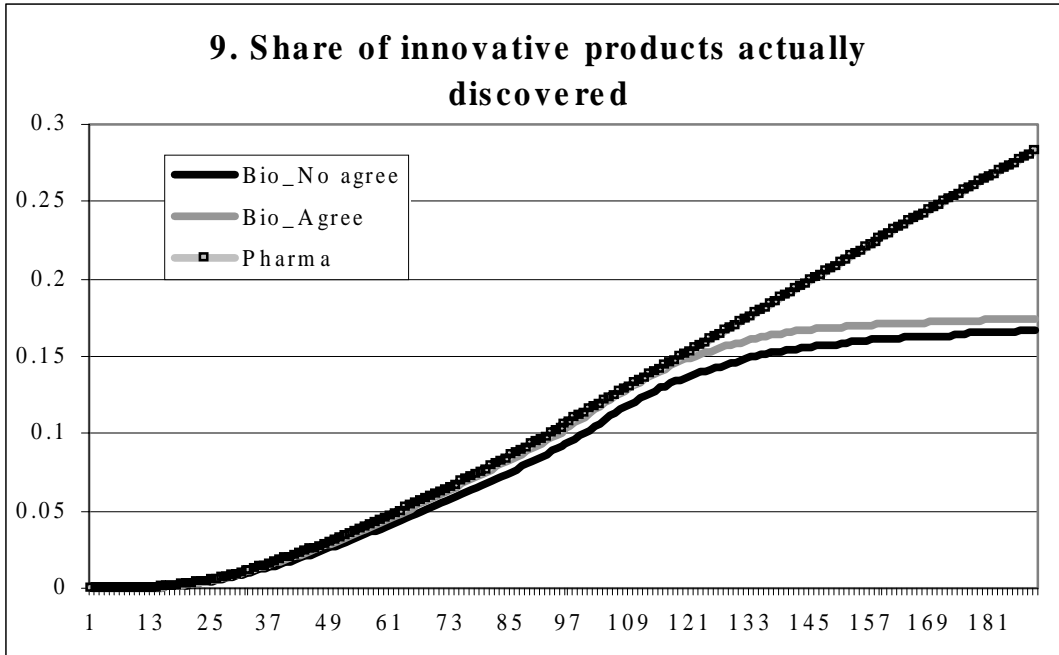


### 7. Average size of alive incumbent firms (budget)

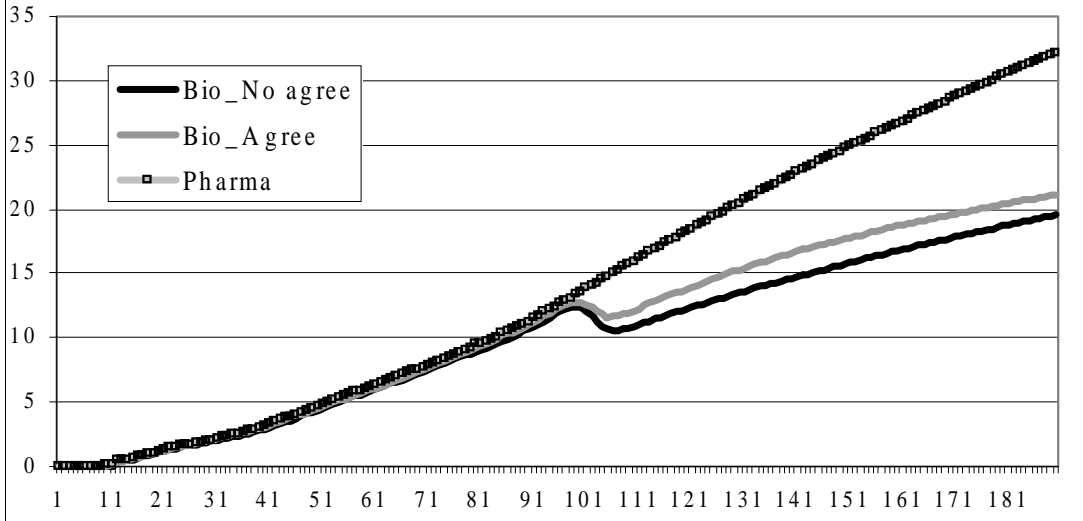


### 8. Average size of alive NBF (budget)





**11. Average number of TAs reached by each firm (out of 100)**



**12. NBF in agreements (overall and without own products - agree sim.)**

