"Entrepreneurship, Innovation and Economic Development"
Feng Chia University, Taiwan 2005

Innovation and firm size: the case of the pharmaceutical industry

By Roxana Bobulescu and Céline Soulas
Professors Dr
ESC Dijon Bourgogne

Abstract: Using the Evolutionary concept of entrepreneurship, this paper focuses on the economic policy of innovation in the pharmaceutical industry. One important question is addressing the governments of developing countries: is the firm size determinant for the capacity to innovate?

According to Schumpeter, the incentive to innovate belongs to the entrepreneur. His evolving thought on the innovating process launched a large debate on the relationship between returns to scale, market power and innovating capacity. We shall explain the advantages and the disadvantages of a large enterprise in the innovating race.

A cyclical relationship between firm size and innovation can be illustrated in the pharmaceutical industry. Innovation reveals a dynamic process. Various firm sizes coexist at different stages of the technological paradigm (between the origin and the maturity). Learning by doing initiates a virtuous circle, which seems to be larger than the individual firm.

Consequently, the size of the firm is a moving target. Innovation is to be linked with industrial, technological networks. Small firms are cooperating and so increasing returns to scale may appear at the level of the industrial districts. Industrial policies stimulating innovation as a competitive edge should then concentrate on creating strong incentive for small firms to cooperate. Industrial localizations may encourage technological spillovers

Key words: bioclusters, biotechnology, innovation, pharmaceutical industry, strategic alliances, industrial policy.

Preliminary insights

Pharmaceutical industry has been characterized by an important consolidating movement since the late 80s. Scale economies were so important that they accelerated this process during the 90s. Many mergers took place between most pharmaceutical firms due to the rising cost of R&D and the need to attend the critical mass for both R&D and marketing activities.

The consolidating movement is concomitant with an increasing R&D expenditure, an increasing return per drug and many new drugs have benefited society for the last decade.

But, according to a recent paper (Grabowski 2004), in the last 3 years we assisted to a tendency reversal. The number of innovative new drugs has decreased under the historical trend, R&D productivity collapsed. Grabowski considers it as a consequence of patent challenge by generic firms and by political pressures to stop the rise of pharmaceutical expenditures. He believes that recent years have initiated a transition or adjustment phase between two important innovative waves. The persistent struggle to cut costs in pharmaceutical companies may have lasting influence on innovation.

The nature of the innovations of a sector lie within a collective framework that decides on the objective and the resources used to reach it (Dosi, 1982). This is the notion of technological paradigm, according to which the scientific and technological orientations of innovations, as well as the existing resources used to achieve them, define a particular research situation (Kuhn, 1983). The application of this concept to the analysis of the pharmaceutical scene enables us to account for its duality, using chemical and bio-pharmaceutical paradigms, and proves to be very enlightening concerning the process(es) in action. (Schwartzman, 1976 – Gambardella, 1995)

The scientific reasoning resulting from the chemical paradigm lies within a unique logic of trial and error that comes in a variety of forms according to sequential selection procedures. In this framework, the researcher does not know beforehand the effectiveness nor the opportunity of a new molecule (Tollman et al, 2001). The discovery of an innovative drug is the result of a procedure known as the stochastical sorting of molecules without the themes of research being set. The pharmaceutical industry currently aims to go beyond this extraordinary science. The chemical paradigm is coming up against its own scientific limits more and more often, and no longer satisfies contemporary pathologies. The drugs it enables to put on the market usually offer a simple qualitative and/or quantitative improvement by addition, modification or recombination of the features of an already existing product. These products are developed for their commercial value since they usually lead to a reallocation of market share (Barral, 2000).

In this particular context small biotechnological firms appear to contribute more effectively to the innovation process than large traditional firms. Today the biomedical knowledge determines the discovery process. R&D is no longer "random" screening but "rational" or "scientific" drug discovery, with important consequences, as we will see in the present paper.

The first section examines the relationship between firm size and innovative activity in the light of empirical studies and theoretical insights around the "schumpeterian hypothesis", in an evolutionary frame. We shall briefly explain relative advantages of large and small firms in bringing out new drugs.

The second section presents the new innovative structure combining the advantages of the large firm with those of the new biotech companies in project-oriented, cross-competencies partnerships. Early funding by large companies helps new biotech SMEs in their innovative development.

Conclusions will then be drawn concerning industrial policy aimed to support innovation.

How does firm size matter?

There is an abundant literature on what may be called the "Schumpeterian hypothesis", that is the innovative activity as a function of firm size. According to Grabowski (1968) "large firms are responsible for most industrial inventive activity". The "Schumpeterian hypothesis" has also been tested by Scherer (1965), Mansfield (1968).

According to McNulty (1974), there is a widely held misconception that for Schumpeter a large firm innovates more and better than the small one. His paper intended to challenge this idea that Schumpeter connected bigness and innovativeness of the firm. His main arguments were found in Schumpeter's writings.

First, for Schumpeter, firm size was a secondary factor of innovativeness. Wheat counted most was the "entrepreneur" as a pushing force, introducing the "new combinations" in the producing process. The "entrepreneur" holds the major role in the innovative system.

Secondly, firm size seemed less important than its age. Schumpeter believed that the newness of the firm was more significant than its bigness. As the evolutionary theory describes it, industrial background is a continuous process of "creative destruction", of rising and falling firms and industries. As Schumpeter puts it "Innovation still emerges primarily with the "young" ones, and the "old" ones display as a rule symptoms of what is euphemistically called conservatism." (Schumpeter 1939: 97)

Thirdly, another important factor of innovativeness is the competitive behaviour in a given industry. So far as the market structure is concerned, the relevant variable in the Schumpeterian system is the "condition to entry": where the entry of significant competitors appears to be impossible, innovation will be slow; when the entry of significant competitors is possible, innovation will be much faster. Innovations reveal a dynamic, evolutionary process, liked to the emergence of new firm or even to the rise to leadership of new man in old firms. This remark was confirmed by Scherer's finding that the contribution of new entrants to revolutionary new industrial products and processes is very much higher than that of incumbent firms (Scherer1970: 377).

The entrepreneurial elements appear to be the essential factor explaining innovation. Firm bigness is only a consequence of the innovative process, even if the two can be concomitant. What counts - and this is true for bug and small innovation – is the quality and the newness of the entrepreneurship.

At the end of the 90s and still nowadays, scale economies became a particularly exploited topic in economic literature. Numerous studies were aimed to explain the relationship between scale economies and successful innovation. These studies focused on the economic advantages, especially cost advantages of large businesses engaging R&D activities. Our paper will be concerned with pharmaceutical industry data. We think that this topic is highly significant for a research intensive industry such as pharmaceuticals.

The relationship between firm size and innovation has been studied from the point of view of the existence of scale economies in pharmaceutical R&D (Comanor 1965; Angelley 1973; Schwartzmann 1976, Jensen 1987, Graves and Langowitz 1993). These authors have raised the question whether or not new drug development is carried out more productively in larger firms. The results diverge from one another. Moreover, they depend upon the measure of innovation. They built regression models with aggregate data from pharmaceutical companies and were testing the relationship between a firm's new drug output (measured by total sales) and the R&D input (total R&D expenditure or total R&D employees).

Some important limits affect the results. First, aggregation covers a much diversified field of research. Pharmaceutical research is carried on by multinationals, whose activities are also non-pharmaceutical (they are conglomerates). The second limit is the time lag between R&D input and drug outputs, which renders regression models much vulnerable to

measurement errors. However, one important result is the existence of scale economies in pharmaceutical R&D. More precisely, large firms appear to have ceteris paribus an advantage in the R&D. Their research programs are more productive than rival programs in smaller firms.

A study by Dimasi, Grabowski and Vernon (1995) showed that R&D cost per new drug approved in the US decrease with firm size, while sales per new drug increase with firm size. The data come from a survey of 12 US-owned pharmaceutical firms. They estimated R&D costs by considering development costs, development phase lengths and failure rates.

This result is emphasized by a paper published one year later by Henderson and Cockburn (1996).

We can synthesise the advantages of large pharmaceutical firms in conducting R&D as follows:

1) Scale economies in pharmaceutical R&D, particularly at the discovery and preclinical development phases. The R&D cost at these phases represents more than one half of the total R&D expenditure. Scale economies are due to significant fixed costs. Moreover, large firms can benefit from a higher specialization of scientific skills in the discovery phase of new drug innovation (Dimasi, Grabowski, Vernon 1995). There are also cost advantages for large firms in the clinical development process due to significant regulatory and legal expertise, which imply fixed costs and specialization (idem 1995).
2) Economies of scope (idem 1995, Henderson, Cockburn 1996) appear as having a significant weight in the R&D process. Diversified projects are carried out by large firms' R&D programs, with positive internal knowledge spillovers within the firm. According to Henderson and Cockburn (1996), "the primary advantage of large firms is their ability to realize returns to scope: to sustain and adequately diverse portofolio of research projects, and to have become significantly more important as the industry has adopted a more science-based research technology" (p. 33). A given drug can affect several organs in the body; so many applications may derive from a drug discovery. Their number increases with the scale of R&D activities. By taking the shape of portofolio diversification in the R&D area, economies of scope are risk-pooling for large R&D programs. They give large firms the advantage of financing the risky R&D programs within the firm.

The advantage of large laboratories in capitalizing on extensive systematic screening methods and the accumulation of information on the properties of each family lies in their size but also in their accumulated experience over the years. Entry barriers therefore result not only from the large amounts invested but also from years of experience : a hierarchical and routine organization optimises large-scale screening, and it is thus ineffective for these large laboratories to take on researchers who are too innovative or too independent (Bartoli, 2000). In other words, due to this routine way of managing (using the researchers' experience) these laboratories produce medicinal technologies of which they perfectly master the discovery process, therefore limiting all entry opportunities of new firms. This routine system produces more innovation (in volume) which aims to compensate for their rather incremental character (in value) (Le Bas, 1995). Indeed, large firms have more of a tendency to adopt a policy opposed to risk-taking, and therefore favour the technical perfection of existing goods rather than attempting radical innovations. These large laboratories often benefit from a wide range of products, oriented towards a few therapeutic classes, and put them on an international market. Being at the bottom is difficult for small firms because their geographic influence is limited and their financial foundation is often not strong enough to take discoveries all the way to the market.

However, some studies showed that the bigness innovative advantages may be offset by

many advantages of smaller size.

1) Biotechnology firms (Grabowski, Vernon 1994, Dimasi, Grabowski, Vernon 1995) have a less bureaucratic R&D management, which encourages creativity. They exploit discoveries made by university settings. Their organizational structure seems to be more suited for a faster innovative process. According to Schumpeter, their entrepreneurship is a better incentive to innovate, along with their newness as an advantage to drug discovery. If we exploit evolutionary thinking, there is an important issue to be addressed in order to understand the dynamics of the pharmaceutical research-intensive industry.

2) A second advantage (Dimasi, Grabowski, Vernon 1995) is the growing access of small firms to CROs (contract research organization), which help them to conduct clinical trials. Some other studies (Fierman, Kyle, Cockburn, Henderson) showed the positive correlation between research productivity and publicly generated knowledge.

3) There are many data (Henderson, Cockburn) on externalities between firms in the industry, arising from the knowledge spillovers. The nature of knowledge as a public-good has been clearly stated by modern growth theory (Romer 1986, Grossman and Helpman 1991).

With the significant development of knowledge of the mechanisms of life, biotechnologies applied to health are viewed as new medicinal production technologies, and are effectively establishing themselves in the market, just as a new paradigm in pharmaceutical innovation would make up for the loss of impetus of traditional chemical methods (Moreau et al, 2002). Genomics, bio-information technology, high-speed screening or even combinatorial chemistry make up a new group of scientific principles that generalise a more deductive, formal and scheduled logic of research (Ronchi, 1996 – Saviotti, 1999). They offer the possibility of acting not only on the effects of a pathology but also directly on its causes. This is called "rational drug design" : scientists use acquired knowledge of the origin of diseases, the properties and the action of medicinal ingredients to create a molecule that aims to restore the modified balance. The emergence of the bio-pharmaceutical paradigm has aroused a renewal of interest in innovation by enabling the discovery of drugs that the system of chemical thinking would not have been able to develop (Sérusclat, 1999). The products discovered may be assessed according to their interest, no longer commercial but therapeutic, for complex pathologies like cancer, cardiovascular diseases, AIDS or even transplants (Barral, 1995).

The resulting innovative activity is essentially carried out by a multitude of small biotechnology firms called start-ups that are particularly flexible and up with new knowledge of life, and often come from universities or private laboratories (Ducos and Joly, 1988). In a context of technological and commercial uncertainty, it is thanks to an entrepreneurial system and also to the audacity of managing directors in deciding to make the most of new knowledge acquired by a small team of researchers that these small organizations carry out the first applications of bio-pharmaceutical innovations in niches in which the previous technology had been unsuitable

Moreover, many alliances and joint-ventures helped small firms to benefit from large, traditional pharmaceutical firms. They were given access to scale economies. R&D but also marketing costs decreased. These cooperating strategies between biotechnology and traditional firms gave birth to new drug developments (Biez-Tadmon and al. 1992, Grabowski, Vernon 1994).

SMEs and large groups in the pharmaceutical industry: working together to innovate

The pharmaceutical sector is at the heart of numerous integration strategies, which are becoming more and more horizontally driven, i.e. essentially concerning the "marriages" of large laboratories. How can the strategic movements of these merger-acquisitions presently be interpreted? From the point of view of the industrial economy, limiting the reasons for the external growth of global pharmaceutical firms seeking only an economy of scale and stable profit shares is particularly restrictive. These operations of horizontal integration aim to progressively change logics as pharmaceutical laboratories aim to fit into the competitive process of biotechnologies. In particular, although the innovative process of each of the technological paradigms is different, it seems that each one also follows a distinct competitive logic. Competition is established respectively in the downstream and the upstream of research activities, establishing the concentration strategies of firms in two directions: strengthening market power and seeking industrial partners.

As in any environment in which full potential has been realized, the slowing down of scientific discoveries sparks off an intense strategic battle to obtain market share. When firms are no longer able to do this, and are satisfied with preserving their market share and maintaining their growth rate, they look to eat into their competition's market share *(Porter, 1982).* This battle essentially aims to emphasize the prices and the services offered by products, in order to reach more and more knowledgeable customers. For firms taking part in the process of chemical research, it is a question of reaching a compromise between a short-term financial logic and their activity portfolios.

The multiplication of merger-acquisition operations among pharmaceutical laboratories is justified by a continual decrease in the profitability of research and development efforts and marketing, and also the intensification of the resulting competition. The final goal of these operations in this framework is for the company to benefit from a much stronger market power and to avoid competing according to prices or to product differentiation. Another much less discussed interpretation aims to justify these external growth strategies by a laboratory's need to increase its sales capacity centred around a pipeline of more promising incremental innovations (Depret and Hamdouch, 2000a). Indeed, the expiration of a patent for a blockbuster product when the company does not have the scientific nor technical means to discover a new one often forces it to go to its competition to try to find what it is unable to find alone. It is the opportunity for the company to incorporate the leading product of its new partner into its often weak product portfolio. Thus, not only does this capitalist partnership enable the laboratory to improve its sales offer but it also favours cost economies that are industrial (rationalisation of production and research sites), administrative (harmonisation of internal decision-making processes) or commercial (optimisation of product ranges).

A final argument aims to justify the considerable number of merger-acquisitions as the most practical way to reduce the number of rival firms on the market (Derhy, 1997 / Michelli and Kohler, 2000).

These interpretations give these concentration operations a primary strategic dimension of strengthening market power. But they do not account for all of the operations. With the emergence of the bio-pharmaceutical paradigm, innovation depends more and more on creativity and on the flexibility of small biotechnology firms.

We are therefore witnessing a very original strategic adaptation of the large pharmaceutical laboratories, which establish partnerships more and more often with these small independent organisations. Cooperation has become the technological policy that enables these large firms to have access to new technologies and new markets, but also to increase their flexibility facing an uncertain market. Indeed, pharmaceutical laboratories are

faced with being practically unable to acquire this knowledge internally, resulting from the fact that their organizational structure, as emphasized by Schumpeter, makes them incompatible with and slow to change (Larue de Tournemine, 1991). Thus, the competitive game is apparently to reorganise in a sort of "battle-cooperation", with each firm establishing and managing a sufficiently strong portfolio of partnerships to be able to take part in the scientific, technical, industrial and commercial stakes of new biotechnologies. Competition in the field of biotechnologies seems to be evolving towards a wide and collective competition: "it is no longer a question of innovating to compete, but competing to cooperate, in order to innovate together. It is now a race to innovate that is also a race to cooperate" (Hamdouch and Depret, 2000: 15).

Bio-pharmaceutical research-development must now be organised in a different way. It requires such specific and complementary technical and human resources, sometimes going beyond the field of life, that it will only be effective with an organisation that has a research process which is part of an industrial partnership. This race to cooperate becomes even more strategic as soon as the principle of exclusivity plays a role. Indeed, this principle prevents each of the partners that has signed a contract of cooperation to change partners, locking them into the cooperation process. This strategy is becoming even more common as the progress of biotechnological knowledge becomes more uncertain and results in high costs that cannot be retrieved. (Bartoli, 2000).

The competitive process in biotechnological research, which is today oriented towards this race to form partnerships, aims to eliminate vertically organized laboratories that research, develop, manufacture and market their own drugs alone and to rationalize organizational structures in order to make each link in the value chain effective. As a matter of fact, all kinds of research (whether carried out in small firms or in hierarchical organizations) play a role : the research of an individual entrepreneur enables to imagine to possibility of combining technical and scientific elements for the first time. But what this specialist can offer does not always meet the requirements of the industrial implementation of manufacturing processes. Similarly, it can sometimes be noticed that the technical knowledge of manufacturing is lacking and this absence leads to the industrialization of inventions. Thus, in the conception of industrial collaboration, a distribution of roles is beginning to emerge that relies on the coexistence of two fields of creation, that of technical imagination and that of development. In fact, a sort of division of the innovative work is developing, favouring academic organizations for the fundamental research, biotechnology firms for the upstream research stages and large firms for the routine and costly stages of development and marketing. Therefore, biotechnology companies find results in their applied research, whereas pharmaceutical laboratories manage the stages of large-scale commercial development (Gambardella, 1995).

In this logic, merger-acquisition operations play a particular role concerning cooperation strategies. Partnership agreements are multiplying and are therefore reducing the number of potential alliances on the market, thereby explaining the concept of "racing to cooperate" or even "battle-cooperation". The only solution for laboratories that have not formed partnerships with biotechnology firms, and would like to take part in bio-pharmaceutical research activity, is therefore to establish links with or to take over a competitor that has established a portfolio of strong alliances and partnerships. Thus, the growth in size enabled by merger-acquisitions seems less and less to represent a final objective as the bio-pharmaceutical paradigm emerges. They are becoming more a way of anticipating new partners to innovate and participate in the creation of markets for radical innovations. These concentration operations therefore represent only a visible part of coordination strategies at work in the pharmaceutical industry. For a laboratory, it is a question of forming partnerships with others "in order to increase and extend the possibilities of cooperation" (Hamdouch and Depret, 2001).

Trust is essential for these strategic alliances to work. Partnerships should be based upon a precise definition of intellectual property. Therefore they need control and formalization of the processes and routines (Powell, 1996). The advantage is that more flexible and financially transparent project-based operational sequences replace vertical hierarchical structures. Simultaneously, the "projectification" goes hand in hand with a more market-oriented research and development, because "new biotech" are dependent on a specific input and financial support from the "big pharma".

This kind of strategic alliances can be illustrated by Novartis' agreements. The first was aimed to develop Evoscreen with Evotec Biosystems (german biotech company). In exchange for early funding, Novartis benefited from a joint technology with a very dynamic biotech company. The second alliance concerned Novartis and a US biotech Vertex Pharmaceutical in 2000. The alliance created a new model of innovation process – a combination between Vertex integrated parallel drug discovery and Novartis portfolio management system (optimization of early development phase of new compounds and promotion of selected compounds to rapid clinical development). Novartis agreed to pay Vertex approximately $ 600 US million in pre-commercial funds (Zeller 2002).

Conclusion

Industrial policy in France and more largely in Europe focuses on research and development in the pharmaceutical sector, due to its high innovative potential and today biotechnological cutting-edge research. Government intervene to stimulate medical and pharmaceutical research. Subsidies to the biotechnological sector encourage entrepreneurship and innovation. In France, research tax credit and tax exemptions may be granted to SMEs having less than 8 years of existence and less than $40 EU million of turnover (Young Innovative Entreprise). Actually, 50% of new drugs are coming from biotech, especially the most innovative ones (insulin, human growth hormones, recombinant growth factors, vaccines, monoclonal antibodies for treatment of cancers, inflammatory and infectious diseases, cell therapies …). We can count 3000 biotech SMEs worldwide (300 around in France).

Moreover, important spillovers between public and private research in spatially concentrated districts or technological clusters have emerged due to the presence of skilled, available workers. Incubator productivity, patent density, Anvar (National Agency for Innovation) aid density in France, the volume of venture-capital investment and the density of the private industrial and technological base are all criteria for site selection. According to these criteria, some large bioclusters may develop in Europe, for example Paris and the Paris area (Palaiseau/Sarclay) for Life Sciences, Grenoble for Bionanosciences and Toulouse for Biotechnologies and Cancer. Such bioclusters already exist in New South Wales (NSW) and Sydney in Australia, California and New York (Hudson Valley Biotech) in US, South East England (around Oxford and Kent).

Important subsidies are directed towards specific industrial location, with cooperating R&D and positive external effects. In this context, firm size is of secondary importance for the innovative process is carried out by project-oriented inter-firm cooperation or benefits from technological transfers inside bioclusters.

Still, geographical proximity is not indispensable, as technological cooperation takes the form of international project contracts between pharmaceutical and biotech. Project teams create organizational and cultural proximity which is crucial for knowledge flows within and between firms. International networks "substitute diminishing spatial proximity with organizational, cultural, relational and technological proximity" (Zeller 2002).

Globally, the strategic target of industrial policies is the biotech SME and public-private cooperation (excellence centres).

References

ANGILLEV A. S. (1973) "Returns to scale in Research in the Ethical Pharmaceutical Industry Some further Empirical Evidence", *Journal of Industrial Economics,* 22:81-93.

BARRAL P.E (2000) *La vie changée : médicament et dynamique technico-économique*, Médicament et Société, Paris.

BARRAL P.E (1995) *20 ans de résultats de recherche pharmaceutique dans le monde (1975-1995)*, Rhône Poulenc Rorer Fondation, Paris.

BARTOLI F. (2001) "Système national d'innovation: caractéristiques et perspectives pour les industries de santé en France", *Education et Formation*, n° 59, avril-juin: 99-112.

BARTOLI F. (2000) *Dynamique sectorielle d'innovation : le cas de l'industrie du médicament en France*, Thèse de Doctorat en Sciences Economiques, Paris Dauphine.

BIENZ-TADMOR B., DICERBO P. A., TADMOR G. and LASAGNA L. (1992) "Biopharmaceuticals and Conventional Drugs Clinical Success Rates", *Bio/Technology,* 10: 521-25.

CAHIERS Industries (2004) n° 100, Nov-dec: 13-22.

COMANOR W. S. (1965) "Research and Technical Change in the Pharmaceutical Industry", *Review of Economics and Statistics*, May, 182: 90

DEPRET M.H and HAMDOUCH A. (2000a) "Fusions et acquisitions dans la pharmacie : les sociétés de biotechnologie sont-elles menacées ?", *Biotechnologies et finances*: 6-7.

DEPRET M.H and HAMDOUCH A. (2000b) "L'économie des nouvelles biotechnologies", *Biofutur,* 200, May: 32-40.

DERHY A. (1997) "Fusions-acquisitions : la logique sectorielle", *Revue Française de Gestion*, January-February: 12-18.

DIMASI J. A., GRABOWSKI H. G. and VERNON J. (1995) "R&D Costs, Innovative Output and Firm Size in the Pharmaceutical Industry", *International Journal of the Economics of Business*, Vol. 2, No. 2: 201-19.

DOSI G. (1982) "Technological paradigms and technological trajectory : A suggested interpretation of determinants and directions of technological change", *Research Policy*, vol.11, 3: 147-162.

DUCOS C. and JOLY B. (1988) *Les biotechnologies*, La Découverte, Repères, Paris.

GAMBARDELLA A. (1995) *Science and Innovation. The US pharmaceutical industry during the 1980's,* Cambridge University Press.

GRABOWSKI H. G. (2004) "Are the Economics of Pharmaceutical Research and Development Changing? Productivity, Patents and Political Pressures", *Pharmacoeconomics*, 22 Suppl. 2: 15-24.

GRABOWSKI H. G. and VERNON J. (1994) "Innovation and Structural Change in Pharmaceuticals and Biotechnology", *Industrial and Corporate Change*, 3, 2: 435-49.

GRABOWSKI H. G. (1968) "The Determinants of Industrial Research and Development: A Study of the Chemical, Drug and Petroleum Industries", *Journal of Political Economy* 76, March-April: 292.

GRAVES S. B. and LANGOWITZ N. S. (1993) "Innovative Productivity and Returns to Scale in the Pharmaceutical Industry", *Strategic Management Journal*, 14: 593-605.

HAMDOUCH A. (1988) "Concurrence et coopération inter-firmes", *Economie Appliquée*, LI, 1: 7-51.

HAMDOUCH A. and DEPRET M.H (2000c) "Coalitions industrielles, réseaux de firmes et dynamiques de concurrence / coopération dans les secteurs en cours de globalisation : le cas de l'industrie pharmaceutique", *Cahiers de la MSE, Série Rouge*, 2000-24, Paris 1.

HAMDOUCH A. and DEPRET M.H (2001) *La nouvelle économie industrielle de la*

pharmacie : structures industrielles, dynamique d'innovation et stratégies commerciales, Elservier, Biocampus, Paris.
HENDERSON R. and COCKBURN I. (1997) Taille des entreprises et productivité de la recherche du secteur pharmaceutique, dans : JACOBZONE S. (Eds), *Economie de la santé : trajectoires du futur*, I*NSEE-Méthodes, n°64-65, Economica, Paris*: 186-210.
HENDERSON R. and COCKBURN I. (1996) "Scale, scope and spillovers: the determinants of research productivity in drug discovery", *RAND Journal of Economics*, Vol. 27, No. 1: 32-59.
JENSEN E. J. (1987) "Research Expenditures and the Discovery of New Drugs", *Journal of Industrial Economics*, 36: 83-95.
KUHN T. (1983) *La structure des révolutions scientifiques*, Flammarion, Paris.
LARUE DE TOURNEMINE R. (1991) *Stratégies technologiques et processus d'innovation*, Organisation, Paris.
LE BAS C. (1995) *Economie de l'innovation*, La Découverte, Repères, Paris.
LUNG N. and RUPPRECHT F. (1997) "Productivité de la recherche et rendements d'échelle dans l'industrie pharmaceutique", *Document de Travail, INSEE*, Paris.
MANSFIELD E. (1968) *Industrial Research and Technological Innovation*, New York: W. W. Norton.
MC NULTY P. J. (1974) "On Firm Size and Innovation in the Schumpeterian System", *Journal of Economic Issues*, Vol. VIII, No. 3, September: 627-32.
MICHELLI J.L and KOHLER P. (2000) "Déterminants et conséquences des Fusions-acquisitions", *Revue Française de Gestion*, 0, 131: 6-19.
MOREAU A., REMONT S. and WEINMANN N. (2002) *L'industrie pharmaceutique en mutation*, Les Etudes de la Documentation Française, Série Economie, Paris.
PORTER M.E (1982) *Choix stratégiques et concurrence : techniques d'analyse des secteurs et de la concurrence dans l'industrie*, Economica, Gestion, Série Politique Générale, Finance et Marketing, Paris.
POWELL W. (1996) "Inter-organizational Collaboration in the Biotechnology Industry", *Journal of Institutional and Theoretical Economy*, 152: 197-215.
RAUGEL P.J (1993) "Les sociétés spécialisées en biotechnologies : stratégies, environnement industriel et financier", dans : Scriban R. (Eds) : *Biotechnologies*, *Lavoisiers* Paris: 773-813.
RONCHI E. (1996) "Les biotechnologies et la nouvelle révolution en matière de soins et de produits pharmaceutiques", *STI Revue*, 19: 21-48.
SCHARTZMANN J. (1976) *Innovation in the pharmaceutical industry*, Baltimore, John Hopkins UP.
SCHERER F. M. (1970) *Industrial Market Structure and Economic Performance*, New York: Rand McNally: 377.
SCHUMPETER J. A. (1950) *Capitalism, Socialism and Democracy*, New York: Harper and Row.
SCHUMPETER J. A. (1939) *Business Cycles*, New York: McGraw Hill, Vol. 1.
SERUSCLAT F. (1999) "Génomique et informatique : l'impact sur les thérapies et l'industrie pharmaceutique" Rapport parlementaire, Office parlementaire d'évaluation des choix technologiques, *Sénat et Assemblée Nationale* 20, 14th of October, Paris.
TOLLMAN P., GUY P., ALTSHULER J., FLANAGAN A. and STEINER M. (2001) *A revolution in R&D : how genomics and genetics are transforming the biopharmaceutical industry ?*, Boston Consulting Group, November, Paris.
WINTER S.G (1984), "Schumpeterian competition in alternative technological regimes", *Journal of economic behavior and organization*, 5, 3-4: 287-320.
ZELLER C. (2002) "Project Teams as Means of Restructuring Research and Development in the Pharmaceutical Industry", *Regional Studies*, Vol. 36.3: 275-89.