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The History of a Deal or How to Win an International Competition in France in the 1970-1990s?

The case of two anti-cancer drugs: Navelbine and Taxotère

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Business Beyond the Firm

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The History of a Deal or How to Win an International Competition in France in the 1970-1990s? *The case of two anti-cancer drugs: Navelbine and Taxotère*

Abstract

The understanding of the dynamics of innovation involves different levels –local, national and international- and fields of analyses. Historical discussions have stressed the heterogeneity of the innovation processes across time, sectors and countries. However, one fact is obvious: during the twentieth century, links between science, technology and innovation became more complex until finally becoming a fuzzy milieu. Today, science and technology constitute a *continuum*. But an issue remains: What do we know about the path, which converts an academic discovery into a business product? What was the role of structures, organisations? How could people act to promote their ideas, processes or products?

In France, from the 1960's to the present day, studies of the relationships between the Academic world and the industrial one through the history of a public laboratory, the ICSN-CNRS (specialized in the chemistry of natural substance studies: one of the main laboratories of the French National Centre for Scientific Research) have enabled to understand how researchers interacted with different milieus that they had to encompass in their work, allowing them to negotiate with business managers.

After presenting first what was the history of this academic and public laboratory and what were the industrial borrowings in the matter of management by the ICSN's directors, I will then focus the second part of this presentation on a study of the path followed by Pierre Potier (team leader who discovered the two anti-cancer drugs Navelbine and Taxotère) to develop cooperation with industrialists. In response to this what was the behaviour of the business people? What was the role of the State in the promotion of the academic results? Conjoining an original management (for a public laboratory) with a tremendous international network (academic as well as industrial), the researchers met success patenting their discoveries: the two drugs were blockbusters.

Even if the history of medicine does a lot to comprehend what has happened in the process of making a new drug especially from a clinical point of view, and even if the study of pharmaceuticals is becoming a new and specific field, very little is known about the history of pharmaceutical industries themselves, purely because of the generally secretive attitude of firms. They restrain the access to the industrial archives. *Aventis-Synthélabo* is still mistrustful and refuses access to the Taxotère archives. However, the pharmaceutical company *Laboratoires Pierre Fabre*, which has developed and produces Navelbine, has accepted the principle of an historical study. Even so, this part of my research is a work in progress; I will try, in the last part of this presentation, to explain what the consequences of the cooperation with the academic research were for this firm. How this cooperation has affected the structure and the organisation of this firm? How has emerged a new strategy? What were the behaviour and the demeanour of both researchers and industrialists? What was the influence, in the long term of what was considered as a new way to search and work for a firm as well as for a public laboratory? But simply, what was the path, which led researchers and industrialists from a national field to an international field of competition?

Introduction

Business history studying the companies of the Second XXth century shows that Science lead and organise all research, development, conception, and production activities. Some of us (scientists as well as historians) speak about the scientifisation process of the industry.

At the same time, governments of the USA, the UK, Germany, France, Japan, the EU, decided to become a major actor in the scientific life leading and promoting science and technology as well, and by implication starting off "the big science" connected to "the big business. It is well known because it was well studied that companies working for and with the national defence services became members of military-industrial complexes creating a general belief that science and technology could and would solve people problems. Very soon, during the 1960s and the 1970s, the trend became wider, including all industrial sectors. This evolution and development made very difficult the reading of this new world become "*a fuzzy complex of actors and actions*"[1].

From the 1960s and the 1970s the French companies that I study showed the process of the interpenetration of academic and industrial world because of national policies and due to the connexion of different knowledge. During the period 1980-2000, the process became more marked although the States were not so engaged in a matter of research policy. The question could be how two opposite positions could have the same effect?

International and national data confirm the interpenetration, enlightening an increasing recourse to the academic research naming this fact 'scientifization' of the industry and an industrialisation or worth considering Science as a commodity (privatization of knowledge, rise of patents in free fields).

Today, science and technology constitute a *continuum* and researchers (academics and industrialists) could be seen as a hybrid population, moving from academic to industrial world, linking them together. But an issue remains: What do we know about the path, which converts an

[1] From A. Tharckray, (ed.), (1998), *Private Science. Biotechnology and the Rise of Molecular Sciences*, Philadelphia, University of Pennsylvania Press, 7, quoted by Strasser B., Bürgi M., (2005), « L'histoire des sciences, une histoire à part entière », in *Revue Suisse d'Histoire*, 55, 3-17, 11.

academic discovery into a business product? What was the role of structures, organisations? How could people act to promote their ideas, processes or products?

After presenting first what was the history of an academic and public laboratory the ICSN (specialized in the chemistry of natural substance studies: one of the main laboratories of the French National Centre for Scientific Research) and what were the industrial borrowings in the matter of management by the ICSN's directors, I will then focus the second part of this presentation on a study of the path followed by Pierre Potier (team leader who discovered the two anti-cancer drugs Navelbine and Taxotère) to develop cooperation with industrialists. In response to this what was the behaviour of the business people? What was the role of the State in the promotion of the academic results? Conjoining an original management (for a public laboratory) with a tremendous international network (academic as well as industrial), the researchers met success patenting their discoveries: the two drugs were blockbusters.

And at last, because the pharmaceutical company the *Laboratoires Pierre Fabre*, which has developed and produces the Navelbine, has accepted the principle of an historical study and even so, this part of my research is a work in progress, I will try to explain what the consequences of the cooperation with the academic research were for this firm. How this cooperation has affected the structure and the organisation of this firm? How has emerged a new strategy? What were the behaviour and the demeanour of both researchers and industrialists? What was the influence, in the long term of what was considered as a new way to search and work for a firm as well as for a public laboratory?

I The Institute for the Chemistry of Natural Substances ICSN-CNRS, an academic and public laboratory in the international trend of science

France, unlike the USA did not have a general project and programme devoted to the eradication of the cancer[2] before 2002. But despite the fact that another national institute the Inserm (national institute for the health and the medical research) worked on medical topics the CNRS (national centre for the scientific research) was involved in many ways: funding different projects, allowing different research teams to search in many directions freely chosen by the laboratories' directors or the researchers themselves[3]. Until the end of the 1990s the researchers' work was characterised by a great autonomy and an important freedom of action.

In 1955, because France had a lot of ground to make up in chemistry of natural substances, the general directors of the CNRS founded the ICSN. French universities were still in a poor situation. So the CNRS was the only research organisation able to create this new laboratory. For political, scientific and cultural reasons (competition between Janot and Lederer's team increased by rivalries between universities and research centres), but certainly because Lederer had regular relationships with the industrial world, the directors general of the CNRS decided to nominate Janot and Lederer as co-directors of the new institute[4]. From that time to 1989 the ICSN had always two co-directors. Pierre Potier (1933-2006) succeeded his master Janot and Sir Derek Barton (1918-1998), Nobel Prize for Chemistry (1969) succeeded Lederer. After that, Pierre Potier and Guy Ourisson (1926-2006, Professor at the Strasbourg University -eastern France- and later President of the French Academy of Science) assumed the co-direction. From 1989

[2] M. Le Roux, V. Walsh, « Contingency in Innovation and the role of National Systems: Taxol and Taxotère in the USA and France », *Research Policy*, vol. 9, n°3, nov. 2004, p. 1307-1327, D. Mowery, « National Security and National Inovatinsystems », *Journal of Technology Transfer and Commercialization*, 34, 2009 , R. Nixon, 'Annual Message to the Congress on the State of the Union, January 22 1971, The American Presidency Project, http://www.presidency.ucsb.edu/ws/index.pho ?pid=3110, consulté le 31mai 2010.

[3] M. Le Roux, « A Chemist's Community as a Forerunner in Management Change and Innovation in France during the Second Part of the Twentieth Century? The Case of the *Institut de Chimie des Substances Naturelles*, *a CNRS Laboratory* », *Business and Economic History on-line* vol. 7, 2009.

[4] ICSN Archives, E. Lederer's speech that he delivered when he received the 'Gold medal of the CNRS' in 1974; E. Lederer, « La chimie des substances naturelles », *Cahiers pour l'histoire du CNRS*, Paris, 1989, 2, 43-54.

until today, it has been directed by one individual: first Pierre Potier, then Jean-Yves Lallemand (1943-) after Potier's retirement and today David Crich[5].

The choice of a co-direction could be seen as surprising but was pragmatic. Creating an alliance between the two most recognized natural substance chemists was the best way for France to regain a place in the international competition. Both Janot and, especially, Lederer were open to the international scientific and industrial world. From the beginning of the ICSN all the researchers were connected to foreign teams, British or Swiss; the PhD students and the researchers regularly had to go abroad. Janot instituted the principle of a real team working, following the Swiss model –far from common practices in France at that time. As for Lederer, he carried on the collaboration with chemical firms either to have funds, raw material or help for development *etc*. Both of them patented some results. The ICSN scientific committee included famous foreign chemists and the ICSN quickly developed international fame. Sir Derek Barton had increased the international ICSN connexions especially with the UK and the USA when he left the CNRS because of French law that imposed retirement on him too. This recourse to industry (either to have funds or raw materials) was the consequence of inappropriate budget, insufficient to properly work. The ICSN was not an exception, but remains the first academic research centre having said that industrial fins was a necessity.

During the 1960s the CNRS' General Direction did not see the issue of having industrial contracts as the ICSN co-directors did. Therefore E. Lederer was bothered, even if the ICSN's researchers were always in accordance with the law and the researchers' statute. So the co-directors did their best to encourage researchers' co-operation with industry and to protect them from the National Research Committee, in charge of individual researchers' assessment and promotion. Later, the top directors of the CNRS changed their mind without taking a real decision. The CNRS general director let the ICSN researchers do what they wanted to manage

[5] He did his PhD at the ICSN, under the supervision of Sir Derek Barton and did a post-doc under the supervision of Potier and Barton.

their relationships with chemical firms. In 1975, the CNRS' general directors concluded an agreement with the chemical firm Rhône Poulenc Rorer to bring about synergy between the public research and the industrial R&D. Trade-union opposition was very strong and unionists argued that the French government wanted "to sell the main French research body to a major capitalist firm". This ambivalent atmosphere endured for a decade or so. Even if this type of contracts met with a more favourable reception in the 80s, Barton did not understand why the majority of his French colleagues were suspicious when he talked about industrial collaboration. For him, it was obvious that natural substance chemistry could not progress without the help of industrial research, which had greater means for the research development than the CNRS. Like Lederer before him, Barton was used to work with chemical firms. He did so with open-mindedness because this type of collaboration was more common in Britain than in France. So Potier did his best too, to pursue and increase the international ICSN network based on academic and industrial relationships.

The evolution was less evident for the National Research Committee in charge of academic researchers' assessment and promotion. Publishing remained the sole criterion while patenting was not especially favoured. From the 30s until today, it has been uncommon to meet "public sector scientists" able to admit easily that academic research has had many contracts with industry for a long time, even though since the naught years, the French government supports these connections between academic and industrial research. In 2005, it was still difficult to promote the career of a researcher who had links with industrial R&D and even worse, if the researcher collaborated with enterprises[6]. However, the independence of the laboratories'

[6] Jacqueline Belloni's account, Paris, May 27th 2005. She is 'Director of research' emeritus at the CNRS in the laboratory of Chemistry and Physics at Orsay-University. She regularly worked with Kodak and Fuji because of her discoveries. Just before her retirement, a CNRS manager told her that she did not have the academic career that she could expect because of her industrial relationships. Eric Chol, "Le naufrage de la recherche", *L'Express* news magazine, 20.08.2000 where Jean-Marie Laborde from Grenoble, who patented with his team geometry software that gave a return of 4 millions of FF in 2000 to the CNRS, was presented as a traitor during a congress because of his research contracts with Texas Instrument.

management and the autonomy of their researchers, which were both really highly developed at the CNRS, allowed the expression of a daring idea.

To conclude this first part of my presentation, I would like to stress the following points: the CNRS was the major and main place to do research what ever the discipline could be, even if French universities were on the way to develop their own capacities. Means and salaries were not very high, in comparison with the USA for instance but most probably because of the weak power of the French university concerning the research, the management was a sort of compromise mixing the necessity of producing a high level knowledge and a great autonomy and freedom, allowing all type of strategies. So it was a good place for who wanted to have an academic carrier, especially for determined and daring people. This organisation was in my opinion a key element to reshape the French system of innovation after the WWII.

II Science in action: management, patents and success

To understand what happened at the ICSN and why we could consider this laboratory as being a forerunner of a new way of searching, I will concentrate on Pierre Potier's ways and means of discovering new drugs. We must keep in mind that he inherited a prestigious laboratory where a deep cooperative culture was a way to work with industry. Potier's team has discovered two major molecules, patented them and has dealt with at least two firms' Laboratoires: *The Laboratoires Pierre Fabre* and *Rhône Poulenc Rorer* (today *Aventis-Synthélabo*) to turn them into the drugs the Navelbine and the Taxotère[7]. They generated roughly 90% of the royalties paid by firms to the CNRS until 2007, and created a turnover bigger than one billion euros per year for each company. The turnover for Taxotère in 2004 was 1,43 billion euros.

Recruited in 1957, Pierre Potier worked all his professional life, more than 40 years, at the ICSN even though he negotiated means to take other responsibilities on: founding and managing the

[7] The first one is an alkaloid, made after the Madagascar periwinkle, the second is a taxoïd made after a yew, Taxus Baccata.

first mixed laboratories joining the CNRS and the industry run in conjunction with the pharmaceutical firm Roussel-Uclaf (1984-1989) or being in charge of the General Head Office for the Research and the Technology[8] at the Ministry of Education, Universities and Research (1994-1996). He was, until his death in 2006, the only French man who had sold two drugs to the American market.

He had had a dual training as a pharmacist -1957- (which allowed him to keep a lot of good contacts at Rhône-Poulenc, the firm where he did his pharmacist certificate courses) with a doctorate in organic chemistry -1962-. One of his main values was that he always had a collective approach to his work as his master Janot did. He never published alone; he always included all his team members in article credits and in drug patents, precisely quoting his colleagues. He never practised a "lift-signature"[9].

Potier and his team had always the same working pattern. They cleared the way for a new research field, made an exhaustive bibliography and then began to research. Then, before going further, the team repeated colleagues' experiments to confirm hypotheses and then defined a new research field. During this fundamental research period, nobody in the team was allowed to communicate or speak about the work in progress. Potier managed his team, as an industrial manager would have done. No information was released outside the ICSN without his written permission[10]. When the fundamental research phases were completed, he contacted himself pharmaceutical firms that might be interested in the results of his research team. He entered into negotiations only when he was absolutely sure of drug feasibility with his discovery. No industrial manager had ever been associated with the team at the beginning of a research. This strategy allowed him to keep a complete control, firstly of the intellectual property and secondly guaranteeing him an industrial property in case of successful research development. The ICSN

[8] Directeur général de la Recherche et de la Technologie, a sort of deputy minister for the research issues.

[9] I mean that the person in charge of a piece of research could include an author even if he had not worked with the team for strategic grounds not linked to the research. P. Potier did not suffer from narcissist wounds and thought that if he wanted something he had to do it on his own.

[10] M. Le Roux, " Genèse des textes de Pierre Potier, chimiste des substances naturelles ", *Genesis*, n°20, 2003, 91-127.

researchers, especially Potier, used industrial R&D as a complementary service provider for academic research.

In the late 1960s, He started looking for compounds that might have anti-tumour properties because clinicians had told him that they needed to know how active the chemotherapy compounds were. He was internationally recognised as a chemist of alkaloids and had already patented some results. Potier and his team started their search on anticancer substances by looking more closely at the vinca alkaloids, studied before at the ICSN. They 're-worked' for 18 months many published on substances extraction as an exercise in "learning by doing", until they were able to isolate the active compounds easily. At that stage, vinca alkaloids had not been made synthetically. Potier's team was also working on alkaloids from thuja and cinchona and one of their discoveries led Potier to propose a synthetic route for the vinca alkaloids.

Because of this specific training, Potier was also interested in developing some techniques facilitating the every-day research work. So Potier and Guénard invented the "Tubulin Test", a tool determining whether chemicals could act to stop a cancerous activity. The French were the only ones having this precise assessment of the efficiency of a substance. This test was a precious help to decide which research they had to push further.

In 1976, Potier's team discovered that if they made a semi-synthesis of one compound of the vinca alkaloid, this new chemical proved to be active using the Tubulin test. This new molecule showed promise as an anticancer drug. They called it Navelbine. Potier offered his discovery to Eli Lilly's CEO that was already marketing naturally occurring vinca alkaloids, but he was not interested. Neither was Rhône-Poulenc, the firm where Potier had had strong partnerships for a long time, giving him access to some of their analytical equipment and sending him compounds since his arrival at the ICSN. RP had broken off its external investments a few months before because of a major crisis[11] and refused to invest in development researches to produce the

[11] RP was nationalized in 1982.

Navelbine[12]. Because none of the pharmaceutical firms involved in anti-cancer drugs production was interested in the Navelbine, Potier collaborated straight away with doctors for the development phase. After 3 more years of negotiations coming to nothing, he met Pierre Fabre, the CEO of a small French pharmaceutical firm the *Laboratoires Pierre Fabre* and persuaded him to produce the Navelbine drug, even though its firm did not belong to the major group controlling the production of anticancer drugs. Pierre Fabre, l'Anvar[13], Pierre Potier, his team and the CNRS obtained 3 main patents. Navelbine was approved by the French administration for use in France in 1989 and by the American FDA in 1994. Then came the discovery of the Taxotère[14].

[12] It is the most expensive part of the research equal to ¾ of the global manufacturing cost for a drug. That is to say that a firm can spend between 100 and 800 million US $ over 10-12 years.

[13] National Agency for commercialisation of public sector research.

[14] The American National Cancer Institute funded the research for more than a decade without any clear result. Since 1971, Taxol had been known as an active agent, but it was one among others. In 1979, a biologist S. Horwitz and her team reported that Taxol's activity was caused by its ability to stop cell division. They published this result. US Taxol is produced from the bark of *Taxus Brevifolia*, a wild species of yew, which grows very slowly (It takes more than a century to fully mature) (see. Vivien. Walsh, Jordan Goodman, (2001), *The Story of Taxol*, Cambridge, 282).
In France, in the meantime, using the same research method as for Navelbine, Potier's team studied thuja and other alkaloids, realising after Horowitz's publication that it was a real opportunity for them because S. Horwitz's conclusions were not very far from their thuja study. Potier was one of people who saw taxol as perhaps the first in a new family of anti-cancer drugs. The ICSN is located in a park planted with *Taxus Baccata*, a European cultivated yew. At the same time, and by chance for Potier, the yews were cut down to build a road. Potier took all the raw material that his team needed without any objection of the CNRS administration (While the American researchers had have to negotiate with Agricultural and Food administration and ecological movement to obtain raw material). So, Potier ordered to his team to handle and to study precisely all the *Taxus Baccata* compounds from roots to needles. All extracts were given the Tubulin test that determined whether a compound may be active and also measures the level of activity. First they discovered that some 0.5-1.0 grams of taxol could be obtained from a kilogram of fresh needles, while the Americans only managed to get 100-150 mg of Taxol from a kilogram of dried bark. Second, two steps before producing Taxol; they discovered another chemical, ten times more active than Taxol. They named it Taxotère. Finally, in addition, they found a semi-synthetic route to produce taxol. Potier informed François Level, one of his Rhône Poulenc - Rorer colleagues, because he was sure that his first thought was right, the discovery would change the way to cure cancer. Potier knew he could expect huge royalties; he knew very well that the CNRS, a public body, would not be able to afford the development research. Immediately, in 1990, the clinical trials began, but this time, paid by RP-R, which regretted its lost opportunity with Navelbine. The economic stakes involved were too big for the CNRS, so Potier drafted the contract jointly between ICSN researchers, the CNRS and RP-R. The firm received marketing approval for France in 1996 and two years later for the US market. At the beginning of 2005, RPR-Aventis-Synthélabo received marketing approval from the US FDA for the most common cancers (breast, lung, prostate) in first intention (*Wall Street Journal Europe*, 25 January 2005). This case study shows how complementary nature of different structures could be efficient. In one way, Potier's team overcame the competition against the American scientists despite the huge resources available to the National Cancer Institute programme (see Vivien Walsh, Muriel Le Roux, (2004), "Contingency in Innovation and the role of National Systems: Taxol and Taxotère in the USA and France", Research Policy, special issue in honour of Keith Pavitt, 33, 9, 1307-1328)**.** If we compare the scale of the NCI programme and the scale of the ICSN means, the USA was doing what only a country of its resources can do. But without the US research system producing a huge volume of knowledge, the French would not have succeeded so quickly. In fact, Potier likened his team to a commando, in contrast with America's massive army (Pierre Potier Interview with Muriel Le Roux, Paris, 15 September 2003).

Potier's working method is essential to explain his success. It associates a scientific network, a monitoring of academic research as well as R&D, the secrecy, an association with industry and a control of intellectual and industrial properties. Potier inherited his former co-directors' network and had always supported it. He had a very active personal network of academic and industrial researchers and a great understanding of the knowledge and practices in his field all over the world. Regular bibliographic updating was an obligation to monitor scientific research and technological development. The training, as an exercise in learning by doing for all the members of the team to master the way to produce compounds, was another essential obligation too[15]. The fact that the team had to be secretive about everything concerning research in progress was essential. The secrecy allowed Potier to patent the discovery and to deal and negotiate well with pharmaceutical managers. He developed a specific way of publishing that protected the heart of his work[16]. He began to publish or allowed his colleagues to do so only after taking out a patent, never before. Potier always chose the time of the association with industrial R&D and no one ever imposed on him a research topic and rhythm. Potier had a very specific and personal method of managing his team and then the ICSN. It was closer to a style of business management than an academic one, especially in France.

Potier's ability to manage the contracts with the *Laboratoires Pierre Fabre* for the Navelbine and *Rhône Poulenc /Aventis* for the Taxotère is noteworthy, first because he had chosen an unfashionable topic. Anti-cancer drugs were not seen as the most desirable area in which firms might compete. For the firms, it became an economic strategic stake during the 90s. Second, if the CNRS did not fund cancer research in the strict sense of the term, many researchers were

[15] Potier was convinced that practical were as important as theory especially for young post-docs because he said that in chemistry each trial could be a route for another discovery, *ibid*. This manner of work is not far from what is described by Malcom Gladwell (2008) in *The Story of Success*, who argues that the main heroic inventors succeed not only because of their network, knowledge, abilities etc. but also because of the time spent on working on the same topic.

[16] M. Le Roux, " Genèse des textes de Pierre Potier, chimiste des substances naturelles ", *Genesis*, *op. cit.*

working on this point, crossing borders each time that they needed to. He knew that fact and used it to his best advantage.

One main aspect of this story was the high degree of autonomy and freedom of action that the French researchers enjoyed at the CNRS. The heart of Potier's management strategy was to preserve both the public science interest and the interest of the researchers by keeping under control the intellectual and industrial properties of their discoveries. He never wanted to create a start-up because he thought academic and industrial research collaboration to be a necessity because of their complementary nature[17]. Nevertheless, his working principles using business methods (management, business rights as well as vocabulary and manners) were seen as a mark of a guarantee by managers and owners of companies.

If this collaboration with industry gives returns of investments to the public sector, (the licence fees paid by the two firms were huge and for a long period the major patents income of the CNRS) Potier never thought of leaving the public sector even though he always had to fight to obtain his due or to make the central administration respect the law. He believed that his position was a good compromise allowing him to work, as he wanted and with whom he wanted. He knew how to manipulate the French research system, to make an apparently strict system flexible.

Because, since the beginning, all researchers were due to have done a training period in a company during their studies, (in this case the student was a way to create or reinforce links with pharmaceutical companies), they were carefully chosen. But if research rules were very strict, with no autonomy, no publication without the director's permission etc., material conditions (salary, equipment) were good. In addition, ICSN's directors always did their best to find employment for their young doctors. Students wanting to come to the ICSN were numerous filling the Gif-connexion network.

[17] P. Potier, « Pourquoi nos labos prennent du retard », *L'expansion,* news magazine, 21st October 1993.

In conclusion, I would precise previous results that I published before. Today, I am able to defend the idea, that in France the ICSN was not a so peculiar research institute as it was thought. The ICSN was a forerunner, having precociously integrated international academic research rules into its searching way. Afterwards the CNRS' board codified practices and industrial cooperation, reducing in a very real sense researchers' autonomy, bringing in systematic controls and assessments at different levels, regulating and standardising the research practices to sustain the international standards of research and innovation which were thought to allow patenting and business in the majority of cases. In one word couldn't we think that was a generalisation of the ICSN management? This standardisation created some tensions between the ICSN and its central administration (the CNRS board and the Research ministry as well).

III A good use of French public research: A medium size company in action, Les Laboratoires Pierre Fabre

Today very little is known about the history of pharmaceutical industries themselves, purely because of the generally secretive attitude of firms especially when they restrain the access to the industrial archives. *Aventis-Synthélabo* is still mistrustful and refuses access to the Taxotère archives. However, the pharmaceutical company the *Laboratoires Pierre Fabre*, which has developed and produces Navelbine, has accepted the principle of an historical study. Even so this part of my research is a work in progress, I will try to explain now what the consequences of the cooperation with the academic research were for this firm. How this cooperation has affected the structure and the organisation of this firm?

The Laboratories Pierre Fabre were established in 1961, in Castres, (south-west of France), owned by Pierre Fabre, a small-town pharmacist turned entrepreneur. Pierre Fabre started

experimentations (mostly galenical pharmacology innovations) in a laboratory attached to the pharmacy during the late 1950s. He also developed clinical testing in cooperation with university of Toulouse physicists through his personal network. He hired two pharmacists dedicated to new drug developments in the early 1960s. Doing so, he decided to make important investments in R&D, including new three-store building fully equipped for development (Péraudel) in 1968 and several collaborations with regional medical research teams. The recruitment of technicians and young PhD graduates increased. Human resources, R&D programmes, business strategy were under Pierre Fabre's personal supervision. Long before the fashion of organic and vegetal products, he always favoured long-term interest in plant based active ingredients supporting cooperation with farmers in France and overseas (tropical plants). This first period of the Laboratoires Pierre Fabre development was based on discovering and developing new medicines and formulas (but with limited patenting, limited industrial capital).

The growth strategy aimed at reaching a critical size, relying heavily on external growth and product diversification (30 employees in 1962 to 4000 in 1989), emerging fields of expertise and notoriety (natural products, cardio-vascular diseases, cosmetics) with the advent of commercial successes. So the company became more structured in its main functions: production plants, research centre, commercial networks and international locations. As a matter of fact, in the early 1980s the Laboratoires Pierre Fabre became a medium size firm with two main activities: pharmaceuticals and cosmetics.

But meanwhile, the pharmaceutical industry was fast changing with the emergence of the blockbuster model and a much stricter and standardized regulation based on the American FDA standards. This evolution favoured the concentration of this industrial sector while the discovery of a new therapeutic agent became increasingly demanding, costly and long. This new international and global context implied a rapid transformation of Pierre Fabre Drug policy

towards a drug discovery model (a Science based process of discovery and drug development) and a business specialisation around few medical topics (cancer, central nervous system, cardio-vascular diseases). It implied a heavy R&D investment what *LPF* did by devoting, in average 20% of its turnover to the R&D. In this very competitive context promoting the relationships and links with the French academic research was a solution…

At the same time Maurice Ponte the head of the ANVAR (French national agency for the development of the research) got in touch with Pierre Fabre. This agency, founded in 1967, had to promote the academic results to businessmen and industrialists allowing future development. Ponte wanted to promote the ICSN discovery due to the insistence of Pierre Potier who did not want to give his discovery up. It was not so difficult to persuade Pierre Fabre to pay attention to the Navelbine. The ICSN had already some research contracts and some of ICSN alumni were working for Pierre Fabre[18]. According Pierre Potier[19], the first meetings were decisive. Through his company, Pierre Fabre easily found people able to assess this discovery (chemists and biochemists, coming from the ICSN, physicians, clinicians…)[20], and providing scientific information as well as complementary and informal ones about the culture of the ICSN without giving a piece of information to his competitors.

After that first step of mutual assessment, things went as quickly as possible. The CNRS, after Potier's proposal, made an agreement with the *Laboratoires Pierre Fabre* in 1982, taken up the agreement made between the "two Pierre". Seven years were needed for the transforming of the vironelbine (the ANVAR/CNRS patent - 1978) into the Navelbine shared out between French hospitals. In 1989, the regulation for therapeutic goods was given for France, between 1991 and 1997 for the European Union countries, in 1994 for Canada and the USA, followed by Japan in

[18] M. Le Roux, « A Chemist's Community as a Forerunner in, Management Change and Innovation in France during the Second Part of the Twentieth Century? The Case of the Institut de Chimie des Substances Naturelles, a CNRS Laboratory », in *Business History on Line*, URL:http://www.thebhc.org/publications/BEHonline/2009/leroux.pdf

[19] Interview MLR – Pierre Potier 2003

[20] Interview, MLR, Yves Le dieu, Nathalie Barondiot et Stylianos Mamatas, Laboratoire Pierre Fabre, 21 June 2010.

1999. In 2001, the Laboratoires Pierre Fabre patented an oral form of Navelbine, improving the well-being of patients during the chemotherapy cures.

Potier failed in convincing other pharmaceutical companies producing anti-tumoral drugs, so the CNRS did not take a risk. It was quite different for Pierre Fabre. His company was a national medium-size firm, with no department of oncology. This agreement meant for LPF displaying a new national and international strategy. It was a bit tricky because LPF began to produce a new alkaloid drug when major American companies had refused to do it (Ely Lilly Laboratories for instance).

I can say, at the first sight after the reading of Pierre Potier's archives, that good conditions were gathered for a success even if the historian must keep a cold mind and some distance.

Many common affinities and similarities linked Pierre Potier and Pierre Fabre and the ICSN and the company as well. The two men had the same vision and approach of what could be the research process studying natural substances. They thought of the research as a continuum from basic research to development. But it could only work if a strong and continuous cooperation between the academic and the industrial worlds happened. Secondly they shared the same interest and knowledge: the natural substances, one for medical purpose the other for cosmetic one. Thirdly, they had the same state of mind, favouring personal and human relationships, local producing units even if they were always ready to go abroad to sustain their ideas and discoveries and dealt with new partners. Both of them had a strong national and international reputation most probably based on a fast capacity to make a decision. This mutual knowledge was based on a human network supplied by the ICSN teams as regards alumni leaving the Institute to be employed by LPF or Ph D contracts or specific research made after a demand.

After the agreement, Pierre Fabre gave his collaborators means to develop this new activity, increasing strongly the R&D capacity, building two new plants in Gaillac and in Pau (still in the south-west of France) and then later founding a research centre in immunology allowing

researches completing the oncologic ones[21]. But the *LPF* board decided to push the adventure further and built those new equipments following the high standard norms of the American Food and Drug Administration. As a result of which, the company was allowed to export the Navelbine in the USA and everywhere in Europe and in Japan.

This choice imposed new technological research perfecting new industrial plants in collaboration with constructors. Furthermore, concerning the production itself, the will of following the American certification process lead the LPF managers to have a stable periwinkle supply (the plant used to extract the substance used for the Navelbine) and to ensure of high quality. It meant once again creating a very specific raw product network based on the quality of the relationships between producers from the tropical zone and LPF and this far before the concepts of sustainable development and equitable market.

I would like to stress the fact that the global approach characterizing this part of the LPF history was not so common for medium size companies in France during the 1980s. Choosing the American certifications when it was not an obligation in Europe was a strategic choice that would provide a very good position in a very competitive market. But the wager was dared.

The decision of producing the Navelbine implied a new industrial orientation, a strategic redeployment and a consolidation of the corporate culture based on shared common ethic values where the cooperation with the academic and public research was the heart. The professionalization of each profession and job increased a lot and the research activity remains the heart of the company regarding the anti-tumoral products as well as the over the counter drugs or the dermatology-cosmetics products. The specialization in limited research sectors (oncology, central nervous system, cardio-vascular diseases and dermatology) was a choice so investments were focused on few innovative molecules (vinorelbine, monitrates d'Isobine, vinflunine). But more than everything, if we consider the fact that pharmaceutical companies are

[21] Today, LPF have 11 research centres (often in coopération with the CNRS and French universities).

research organisations as well as industrial ones, the very specificity of the Laboratoires Pierre Fabre is the weight of the cooperation with the academic and public research centres. These partnerships are materialized today by the creation of mixed research centres (PLF/CNRS) located on PLF sites or at university (CNRS/PLF/university)[22].

This first approach to this history could be interesting especially to understand what could be the role of the small and medium size companies in the process of innovation. This success story is based on original choices: as said previously, the central position of the R&D based on partnerships with academic research, a will to establish producing sites in France, well-targeted industrial and international alliances and a very specific financial organisation[23].

To sum up, we can stress the fact that, for LPF, the cooperation with the academic research and more specifically with the ICSN modified the company perimeter with the creation of the Oncology department, an increase of research centres, a systematic 'use' of a high level research even in cosmetology. This broadening was possible because the ISCN culture was very close to the LPF's one and not only in a matter of research content but also concerning the way to work based on trust in people and a mutual respect. It explains why today the *Laboratoires Pierre Fabre* are part of the *Canceropôle of Toulouse*.

Complementary research through the *Laboratoires Pierre Fabre*'s archives must be done to confirm the general frame of this story. Nevertheless, talking about the history of innovation in Europe during the second part of the XXth century a new pattern seems to be emerging where the cooperation between medium size firms and academic research could have been more efficient that what we know until today.

[22] PLF spent on average, since 1980, 20% of its turnover in research. In 2009, 28% of the turnover was spent for the medical research and 5% for the dermatologic and cosmetic one.

[23] Pierre Fabre foundation hold 65% of the shares, the employees 6% and the remaining belongs to Pierre Fabre himself.

Conclusion

What could we conclude from this short story? Many things must be done to understand what was the share of medium-size pharmaceutical companies in the general process of innovation during the second part of the XXth century because, as Alfred Chandler wrote, an historical case study may have a general range "because the long view reveals clear patterns of success and failure based on real experience"[24]. So, even though we are indebt to the great historian this type of research could strongly qualify or complete his approach.

In his last book he reviewed the evolution of the modern chemical and pharmaceutical industries until the last decades of the XXth century. But France was not precisely described, due to the fact that there are few English versions of the French Business history. In his chapter 11, p. 294 A. Chandler wrote that "During the 1980s the French produced less than 1% of pharmaceuticals sold in world market", that is most probably very true from the point of view of multinational firms. But, if we cross European and American informations, we could qualify his comment.

For instance, it is very difficult to find the French origins of the Navelbine and the Taxotère in the USA databases though that drugs are marketing on the North American market, meaning that the FDA made complete enquiries. It is very difficult to find a mention of French teams' results in Academic journals. The *Laboratoires Pierre Fabre* which are a medium-size company, chose the joint venture strategy with BMS to market the Navelbine in the USA, opening the American market but the French firm is seldom quoted in the scientific reviews, (as are Aventis and the Taxotère) even if the French researchers of LPF wrote and are still writing their papers in English. In addition, it is impossible to find a mention of the *Laboratoires Pierre Fabre* as a partner on the BMS website, even if the FDA has regular contacts with this French company to manage the American stocks of the Navelbine for the American hospitals. These

[24] *Shaping the Industrial Century,* Cambridge, Harvard University Press 2005, p. 312.

examples explain why A. D. Chandler wrote this comment and justify a study on medium-size companies if we hope to have a more precise knowledge of what was and could be the international competition. Despite this silence, the Navelbine and the Taxotère remain among the most used anti-cancer drugs in the world…