

Patents, modular innovation processes and distributed entrepreneurship: The case of genetically engineered vaccines

Antoine Bureth* and Julien Pénin*

This draft: 13 of September 2006

Paper prepared for the DIME *conference* held in London, September, 14-15 2006

Work in progress: please do not quote without the authors' permission

Abstract

Empirical studies indicate that firms may strategically use patents in many different ways (Bureth *et al.*, 2005). In this paper, which focuses on the development of genetically engineered vaccines, we suggest that patents are central elements to structure the development of collective innovations. Specifically, we show that the development of genetically engineered vaccines can be decomposed into three broad and relatively autonomous modules (antigen, vector, adjuvant). The production of a GEV requires combining one element from each module. We argue here that patents are essential to ensure the integration of the different modules and therefore to develop the finite product, i.e. the vaccine. Despite inevitable conflicts, patents improve the interactions among firms involved in the development of innovative vaccines. Far from being a mere tool of exclusion we can therefore consider patents as architectural elements of modular innovations, conveying distributed entrepreneurial incentives.

Keywords: Intellectual property rights, biotechnology, modularity, collaboration, collective innovation

JEL classification:

1. Introduction

Following the seminal work of Arrow (1962), traditional economic theory presents the patent system as being essentially a device to exclude potential competitors. Production of innovation is subject to appropriation failure –because innovators cannot prevent imitators from using their innovation, which decreases firms' incentives to invest in innovative activities. This justifies the implementation of a patent system which, by restoring appropriation, would increase incentives to innovate while not decreasing the diffusion of the knowledge underlying the innovation (since innovators are required to release a description of their innovation in order to be granted a patent). According to this traditional view, a patent is therefore only a tool devoted to increase incentives to do research and firms use the patent system only to exclude potential imitators and to secure of a monopoly rent.

* BETA, CNRS-UMR 7522, Université Louis Pasteur Strasbourg I, 61 avenue de la Forêt Noire, 67085 Strasbourg Cedex, France. Corresponding author's e-mail: penin@cournot.u-strasbg.fr

This work is part of a wider project on DNA vaccine called MIDEV (“Modularité et Incitations dans le Développement de Vaccins AND”) and financed by the CNRS – INSERM - MiRe – DREES in the frame of the program “Sciences biomédicales, santé et société”.

Yet, this view is far too narrow. Empirical studies show that, pharmaceuticals put apart, firms do not consider patents as useful devices to appropriate their innovations, which means that patents do not necessarily increase incentives to invest in research activities (Scherer *et al.*, 1959; Taylor and Silberston, 1973; Mansfield, Schwartz and Wagner, 1981; Levin *et al.*, 1987; Arundel and van de Paal, 1995; Goto and Nagata, 1996; Cohen *et al.*, 2000; Sakakibara and Branstetter, 2001). The recent upsurge in patent application¹ must therefore find another explanation than firms' willingness to appropriate their innovation and exclude rivals (Kortum and Lerner, 1999).

We believe that patents play a much more complex role, beyond the traditional appropriation and incentives concerns. Firms may strategically use patents in many different ways (Jaffe, 2000; Bureth *et al.*, 2005). Empirical studies suggest that firms attribute value to their patents portfolio not necessarily to enjoy a monopoly position but rather to signal competences and strategic positioning, to improve their bargaining power in negotiations, to access to complementary technologies through exchanges and licensing, etc. In short, if they can be devoted to the exclusion of imitators and the protection of a market position, they also support development processes by facilitating the coordination of collective innovation activities (Cohendet *et al.*, 2006).

In this paper, we focus on the role played by patents in the development of Genetically Engineered Vaccines (GEV). This field is worth investigating since vaccines may offer a promising application field for genomic technologies, especially for approaches and tools developed in gene therapy. GT has raised huge hopes from a theoretical perspective but, due to several negative and unexpected results during clinical trials, the approach now raises some reluctance. Scientific and technological unresolved problems as well as a negative perception by the general public prevent financiers from investing in the sector. Yet, it is widely acknowledged among scholars that one technological trajectory that is still promising deals with the development of vaccines using DNA techniques. In 2001, a Canadian foresight study identified the top three ranking genomic-related biotechnologies as molecular diagnostics, recombinant vaccines and vaccine and drug delivery (Daar *et al.*, 2002). The two latter clearly offer important clinical potentials for gene therapy.

It is thus important to understand the main characteristics of the innovation process concerning GEV. Specifically, we show here that those new vaccines exhibit a modular structure, since they can be decomposed into sub-products that can be considered almost independently. The interviews highlight several elementary bricks to combine in order to bring a reliable vaccine on the market. In short, in the development of GEV one can observe three types of modularity: technical, cognitive and organizational modularity.

Considering the product and its functionalities – once could refer to technical modularity – a GEV gathers together three modules: the vector, the antigen, and the adjuvant. Compared to “traditional” vaccines, the biotechnologies generate therefore a decomposition of the product, leading to an increased division of labor in the production. To the same extent, those new vaccines result from the combination of pieces of knowledge belonging to several (and almost autonomous) fields of scientific investigation: cellular biology (production of proteins), molecular biology (production of plasmid), chemistry, biochemistry (fermentation, purification processes), pharmacology (bio-distribution, toxicology, histology), virology

¹ The last ten years have exhibited a drastic surge in patenting, with the total number of patents recorded by the EPO and the USPTO raising from 100 000 to more than 300 000 during the 1990s (Vignier, 2002). The phenomenon has been observed worldwide, although national and sectoral differences remain.

(production of vector), bacteriology, immunology, genomics, proteomics, etc. The span and the variety of the fields of knowledge articulated in research – we talk about cognitive modularity - constitute one of the distinctive features of the R&D processes in biotechnologies, and explain the need for a collective and interactive mode in the resolution of problems. Finally, a kind of organizational modularity can also be observed, with different institutional entities operating at different stages of development, under different risk intensities, time scales and cost levels. We have observed that each vaccine project assembles academic research centers, biotech firms and pharmaceutical big sized firms. Even if closely related, each partner pursues independent objectives, under specific rules, generally summarized through clear work packages and milestones.

The production of a vaccine requires combining elements from different modules, at each level – technical, cognitive, organizational - and the quality of the interactions among the different modules is therefore central since it may foster or prevent the development of the project.

Our interest in this paper lies in the role played by the patent system in this complex modular process. Do patents improve or damage the interactions among players involved in the development of new vaccines? Usual arguments focus on the conflicts that may be induced by patents, on their potential for exclusion and knowledge protection. In clear, they attribute a rather negative role to patents with respect to the interactions among actors of the innovation process. Yet, we claim here that patents are central to ensure the integration of the different modules and therefore to develop a vaccine. Despite inevitable conflicts, we show that patents improve the interactions among firms involved in the development of GEV. Without patents firms would find it much more difficult to collaborate and to articulate their competences, making the vaccine production much harder. Far from being a mere tool of exclusion we can therefore consider patents as being structuring elements of modular innovations. In other words, we propose a vision of patents as devices of co-opetition. On the one hand patents allow their owners to compete within each module. On the other hand patents improve the interactions and the collaborations among the different modules. In both cases they “flag” the innovation development paths and are instruments of incentives and interaction.

Our theoretical analysis of the role of patents as structuring elements of collective innovation is supported by several interviews of French actors in the field of GEV (Start-ups, Public researchers, capital venture, etc.). The interview campaign -actually still under course- is realized in the frame of a project entitled MIDeV (Modularity and Incentives in the DEvelopment of genetically engineered Vaccines). The aim is a better understanding of the collaborative innovation process in GEV and especially of the role of the patent system. The outcome of the 16 first interviews confirms the central role of patents to structure innovation in GEV. Yet, although they provide rich qualitative insights, those interviews cannot actually be used as a basis for a quantitative study.

In the first section we define the main technical characteristics of GEV and we describe the economic features and perspectives of the sector. Then we focus on the modular structure of GEV. We present the different modules and study their interaction. In the third section we analyze the role played by the patent system in the development of GEV. We conclude with general comments on the role of patents as structuring elements of collective innovations.

2. Economics and technical aspects of GEV

2.1 Definition

Prior giving a definition of GEV it may be necessary to remind to the reader what a vaccine is exactly. A vaccine is an antigenic preparation used to produce active immunity to a disease². In other words, a vaccine stimulates the production of antibodies and therefore enhances the immune response of the organism against diseases. Vaccination techniques use the natural tendency of our organism to destroy unknown foreign agents³. The immune system recognizes vaccine agents as foreign, destroys them, and memorizes them. Then, the re-appearing of the pathogenic agent triggers a immune response. The main characteristic of vaccines is thus to induce an endogeneous protection. What is brought from the outside is just the substance (a killed pathogenic organism, or an attenuated form of that organism, or the pathogenic part of that organism) that will help the body to improve its defence.

In this sense vaccination consists of developing active immunisation. It differs from passive immunisation that consists of producing antibodies outside the organism and then to introduce them into the organism to trigger the protection. A central difference between the two is that passive immunisation offers a limited duration (antibodies that have been introduced within the organisms do not last indefinitely) while vaccination is unlimited in time since the organism has learnt to build its own protection.

Conversely to traditional vaccines, GEV use DNA manipulation to trigger the immune response. Hence GEV may (or may not) mobilize gene therapy technics, which consist of introducing genes into an individual's cells and tissues in order to treat a disease. Gene therapy aims to supplement a defective gene with a functional one. The purpose is either to enhance the production of a protein that would be missing or on the contrary to inhibit the production of a protein that would be over produced. These therapies date back to the discovery of American researchers who found out that nude DNA injected into a cell had the property to code for specific proteins without integrating permanently the genome of the cell (i.e. without provoking permanent hereditary changes that may be difficult to control).

With concern to vaccine production, instead of introducing directly the antigen within the human body, gene therapy allows introducing the genetic material into a cell in order to produce within the human body the antigen that will then stimulate the immune system of the patient. It is not the antigen that is injected to the patient but the DNA fragment that will code for this antigen. In short, it is the patient's own cells that produce the vaccine.

Another possibility offered by DNA techniques is to use transfection techniques in order to produce the antigen ex vivo, using specialized cell (bacteria, but also plants or animals). The

² The principle of vaccination dates back to E. Jenner, who observed in 1796 that milkmaids would sometimes become infected with cowpox through their interactions with dairy cows' udders. Cowpox is a mild relative of the deadly smallpox virus. Jenner had thus the idea to take infectious fluid from the hand of a milkmaid and inserted this fluid, by scratching or injection, into the arm of a healthy local eight year old boy. The later then showed symptoms of cowpox infection. Forty-eight days later, after the boy had fully recovered from cowpox, Jenner injected some smallpox-infected matter into him again, but this time the later did not show signs of smallpox infection. He had developed himself his own protection against the disease.

³ Every human being has its own immune system, which protects an organism from outside influences. When the immune system is functioning properly, it protects the body against bacteria and viral infections, destroying foreign substances. If the immune system weakens, its ability to defend the body also weakens, allowing pathogens to grow and flourish in the body.

antigenic protein is thereafter isolated by purification, and administered to the patient, in order to activate an immune response.

A peculiar feature of GEV is that they can be preventive or therapeutic. In the case of cancer, for instance, current research try to develop processes that would allow a person's immune system recognizing and destroying malignant cells without harming normal cells⁴. Such cancer vaccines are considered as an immunotherapy, i.e. they are based upon the concept of stimulating the immune system to achieve a therapeutic goal. Unlike prophylactic vaccines against diseases such as polio, influenza, and tuberculosis, they are not preventive but must be administered after cancerous cells develop.

In conclusion, compared to traditional vaccines, GEV are attractive due to their simplicity (in the theoretical principle), robustness and wide scope of application. They use relatively standard genomic techniques that can theoretically be applied to the vaccination of many diseases. Second, the active compound is a simple piece of DNA, which is relatively cheap to produce. Yet, since important quantities may be needed in case of human beings, this advantage in term of price is still unclear. Furthermore, some GEV (especially pure DNA vaccines) can be stored over long period of time and, conversely to traditional vaccines, they do not need refrigeration, making them very attractive for developing countries. Finally one of the main advantages of GEV as compared with traditional vaccines is the diminution of the risk for the patient, since there is no need to inject the pathogen agent within the organism in order to develop a protection.

Yet, one of the main problems of GEV vaccines is the carriage and delivery of genetic material into the cell's nucleus. This problem can be decomposed into several steps, each of them corresponding to the crossing of a specific "cellular barrier": The first difficulty is to enter the cell, i.e. cross the membrane, which envelopes the cell and controls what moves in and out. The second difficulty is to carry the genetic material within the cell in order to reach the nucleus. The third difficulty is to enter the nucleus and to maintain the genetic material inside the nucleus. At this step two alternatives are possible: either the genetic material introduced into the cell does not integrate with the genome of the host cell and merely orders the production of the needed protein; or the DNA integrates within the cell's genome and may conduct to permanent hereditary consequences. The crossing of these different borders is complex also due to the huge quantity of DNA needed for inducing immune responses. The production and purification of large quantity of DNA is not only costly but also increases the risks of side effects. This may explain why, to date, most DNA immunization studies have been carried out in mice. Results obtained were promising but have not been reproduced on human beings yet.

2.2 The market for vaccines

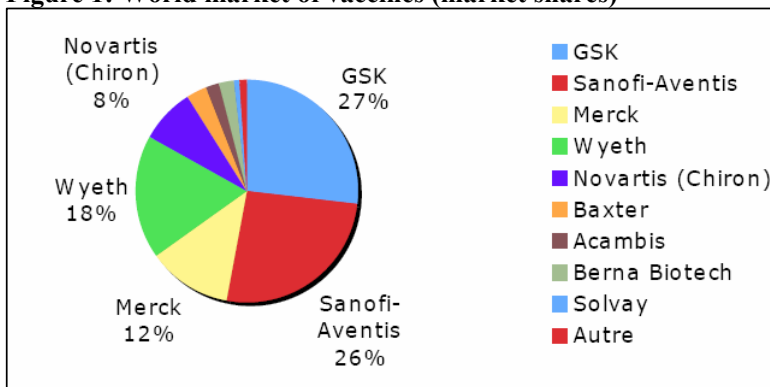
The market for vaccines is very segmented and concentrated, with only few big players that are all divisions of global pharmaceutical houses (Merck, GSK, Aventis, Wyeth and Novartis). Those major vaccine producers generate around 85% of the sector's sales⁵. To

⁴ Cancer proliferation within the body is due to the fact that the immune system is not able to recognise tumorous cells. The purpose of a vaccine is therefore to mark the tumorous cells so that the immune system can recognise and destroy them.

⁵ Datamonitor, Strategic Perspectives: Vaccines (2003).

compare, in 1955, 18 firms shared the market. The principal focus of the actors in this field is paediatric vaccines, which represent about 70% of the market⁶.

Figure 1: World market of vaccines (market shares)



Sources: Datamonitor (2003)

Now, some specific features of the vaccine market must be underlined (Danzon *et al.*, 2005). They explain the peculiar industrial structure that is actually observed (specialization of one or two producers per vaccine/per country), and they generate strong incentives toward the development of new types of vaccines, mobilizing advanced genomic technologies. Vaccines markets are small “by definition”: contrary to what is observed for the treatment of chronic illness, the longer the efficacy, the smaller the demand. Furthermore, cultural habits and national regulation mechanisms keep the vaccine markets country- (and sometimes regional-) specific.

The public intervention, which exists in many countries concerning vaccines against the principal contagious diseases, causes a concentration of the demand and a reduction of the prices. As a result, profitability is reduced and the competition between recommended and non-recommended products is difficult. Furthermore: “market dominance in vaccines is related to product superiority for the majority of patients, no to first mover advantage. By contrast, in many drug classes, multiple products coexist because each product works best for a subset of patient” (Danzon *et al.*, p. 711).

Vaccines aim at treating large number of healthy people. Consequently the risks of liability are largely increased compared to therapeutic drugs. The trials must be conducted on a very large scale to demonstrate absence of rare events, and the financial consequences of a failure are higher than in standard therapeutic approaches. Costs of development of new vaccines are increasing, especially due to safety requirements from the public authorities. Clinical trials are estimated to account for 45% of the total R&D budget for drug development in 2003. Those threats have caused the retirement of several vaccines producers.

Thus, vaccine producer must deal with a strong scissor effect, due to high fixed costs on one hand - estimated to account for 60% of the total production cost⁷ –and to low prices on the

⁶ Scrip Reports, The World Vaccines Market (2002).

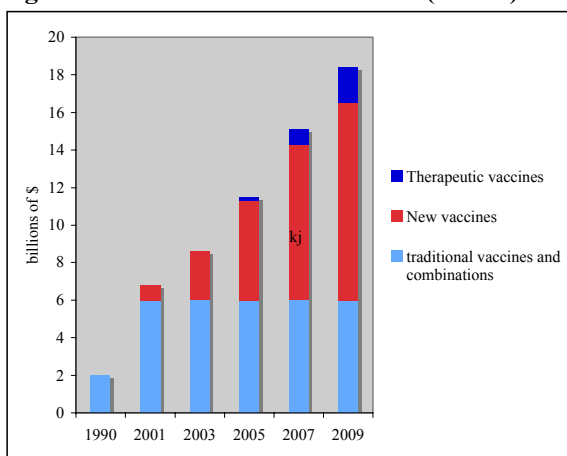
⁷ New constraints on the production of vaccines have also contributed to increase the cost. For instance, the case of Thimerosal, a conservative derived from mercury, whose utilisation has been forbidden by public authorities obliged vaccines companies to fraction their lots, which increase the cost of production and may trigger problems in the management of stocks (penuries).

other hand – explained by limited markets, public price regulation, low-income vaccines users. Two alternatives are possible to solve that tension: the first is to cover the innovation costs by prolonging as much as possible the years of sales. Under that perspective, the vaccines field stagnates for decades, mobilizing few technologies and generating weak revenues. The second is obviously to reduce the production costs of the vaccines, or better said, to modify the production constraints attached to the product. As we will see below, biotechnologies offer such new opportunities on this second path of development.

Indeed, even if it has long been considered as a small segment of the pharmaceutical market, the economic status of vaccines is changing. The bioterrorist threat, the threat of new pandemy (chicken flu for instance), recent progress in cancer research and the impulse given by the non profit sector (the Gate foundation for instance) contribute to restore the image of vaccines and to improve the perspective of this market. The domestic vaccine market in industrialized countries exhibits a drastic increase in pricing. For instance, the price of a dose of DTP vaccine turned from 30 cents in the 80s to \$20 today. In short, “Vaccine manufacturers are increasingly able to capitalize on new products, with some emerging vaccines prices at \$300 or more per treatment course” (Pasternak *et al.*, 2006, p. 112).

Annual vaccine sales have grown from \$2 billion in 1990 to an estimated \$11 billion today. This remains low as compared to the \$550 in 2004 for the whole pharmaceutical market. But the market for vaccine, in opposition to the classical medicine market is expected to grow significantly in the next years. Merck, who will market soon a vaccine against cancer of the neck of the womb, assesses that the overall vaccine market should reach \$18bn in 2009. Similarly, Novartis, who has recently penetrated the vaccine market through the buyout of Chiron, assesses the market to reach \$20bn in 2009. As an example of the new economic status of vaccines, the market has experienced its first blockbuster in 2005, with the sales of the Prevenar® (produced by Wyeth and put on the market in 2000) that have passed 1\$bn sales.

Figure 2: World market of vaccines (trends)



Source: Kaddar M.. (2004), “Vaccine market trends”, international vaccinology training course, Séoul.

Much of the predicted growth of the vaccines’ market is expected to come from the introduction of new vaccines, either against diseases for which no vaccine currently exists or as second-generation products to replace existing vaccines. Given the peculiar features of the vaccine market, there is no room for me-too vaccines. Firms have to be able to decline clearly

differentiated variants of existing vaccines, or to enter radically non-traditional therapeutic areas (cholesterol control or nicotine addiction for instance). There is therefore some place for new biotech firms based on scientific excellence to enter this market and it can be expected that the industrial landscape of the market for vaccines may change in the next few years. One can already see the emergence of new players (Baxter, Acambis, MedImmune) which, despite their small size, may expect strong growth based on innovative products, thus modifying the industrial structure of the market. Nevertheless, new biotech firms will hardly be able to enter the vaccine market without partnering with incumbents (to illustrate the importance of the barriers for the introduction of a new drug, one should keep in mind that the costs of each phase of a clinical trial are multiplied by a factor ten). And each technological innovation, even if improving the efficacy of the final product, will still have to solve the specific constraints in vaccine production, including capacity constraints, quality issues and cost positions.

It is difficult to establish precisely how many GEV are in the pipeline of the industry. The Mercer report (2005) has identified roughly 350 compounds under investigation (188 projects in preclinical development and 158 in clinical trials). The exact share of vaccines mobilizing DNA technologies is hard to assess, But if we stick to DNA vaccines (using plasmid to trigger the production of an antigen by the patient's immune system), a dozen of projects are in human development worldwide, but none has gone beyond phase 2 trials (Forde, 2005), Tacking into account the use of other vectors, or new modes of production of the vaccinal compound, many potential vaccines are in late stages of development (clinical trials phases 2 or 3) and could enter the market soon (Braunagel and Das, 2003). The economic potential for those new types of vaccines is huge since they could pretend to higher prices due to their efficacy to treat important diseases in developed countries (cancer for instance).

3. Modularity and GEV vaccines

3.1 What is a modular system?

A modular system can be defined as a complex system, each parts of which conceived independently but functioning together in a homogenous way (Sako and Murray, 2002)⁸. Modularity refers to the existence of modules (sub-part of the whole system) that when combined together through well-defined interfaces fulfil a global function. The opposite of a modular system is a perfectly integrated system, which cannot easily be decomposed in autonomous sub-systems. Such a conception of modularity is clearly derived from the "loosely-coupling" approach developed by Simon (1962), who characterizes a modular system as "one made up of a large number of parts that interact in a non simple way. In such systems, the whole is more than the sum of the parts, at least in the important pragmatic sense that, given the properties of the parts and the laws of their interaction, it is not a trivial matter to infer the properties of the whole" (Simon, 1962, p. 195).

⁸ In the literature three dimensions of modularity are distinguished: Technical, organizational and cognitive modularity. It is worthwhile to notice that modular decomposition refers to more than just division of labor. The taylorist approach for instance defines a sequence of actions: each sequence mobilizes a domain of knowledge, a specified actor, and bears on a part of a product. But they are not autonomous. A given chronology has to be respected. The content of the different sequences is optimized with respect to the global output of the whole chain. A modular approach expresses rather a sum of local optima: each module is improved, independently from what has been achieved in the other modules. In other words, the division of labor aims at stabilizing practices and learning processes, whereas modularity is fundamentally oriented toward the generation of variety and the introduction of new routines and know how.

A modular system is therefore made up of two things: Modules (subparts of the system) and an interface that ensures the connection of the modules. The aim of a modular system is to achieve an interface that minimizes interdependencies between modules performing different functions. This central point is raised by Koppl and Langlois (2000): “Modularity is not about cutting a system into parts. All systems are already made up of parts. Modularity is about how parts are grouped together and about how groups of parts interact and communicate with one another” (Koppl and Langlois, 2000, p. 18). The central focus is therefore on the ‘right’ number of modules for a system and on the interface that links those modules.

The benefits of achieving modularity are mainly three-folds:

- First, a modular system may spare resources on management. As claimed by Langlois (2002, p. 19), “By breaking up a complex system into discrete pieces -which can then communicate with one another only through standardized interfaces within a standardized architecture- one can eliminate what would otherwise be an unmanageable spaghetti tangle of systemic interconnections.” Yet, too much modularity may increase the cost of management since it may also increase the cost of communication among modules. This suggests that there exist an optimal level of modularity for a system.
- Second, since each module can be conceived independently from the others, a modular system is less exposed to perturbations as illustrated by the seminal example of Simon (1962) about the two watch manufactures Hora and Tempus⁹.
- Third, the overall efficiency to fulfill a global goal will benefit from improved learning process. Indeed, modularity leads to separate the learning about the architecture of the system, from the learning about the features of the modules. This dichotomy allows an increase of diversity generated by recombination of the modules, and, along with the previous point, reinforces the capabilities of the whole system to absorb, to integrate and to valorize innovations and ruptures generated locally and incrementally.

Concerning vaccines specifically, modularity helps:

- To manage complexity. The development of GEV relies on an important variety of scientific and technical fields. The actors mobilized are extremely heterogeneous. In other words, the collective innovation process is costly in terms of coordination and transaction costs, and it is almost impossible for a single actor to master it globally. Modularity – i.e. autonomous sub-parts interconnected through stabilized interfaces – is a necessary condition to allow the establishment of leadership, and to align incentives.
- To manage uncertainty. Modularity provides an answer to the attrition constraints, by enriching the portfolio strategy. It limits the impact of dead ends and unexpected perturbation, insofar as it offers a greater variety in the potential paths of development.

⁹ Simon (1962) gives the following example: “There once was two watchmakers, named Hora and Tempus, who manufactured very fine watches. Both of them were highly regarded, and the phones in their workshops rang frequently. New customers were constantly calling them. However, Hora prospered while Tempus became poorer and poorer and finally lost his shop. What was the reason? The watches the men made consisted of about 1000 parts each. Tempus had so constructed his that if he had one partially assembled and had to put it down-- to answer the phone, say--it immediately fell to pieces and had to be reassembled from the elements. The better the customers liked his watches the more they phoned him and the more difficult it became for him to find enough uninterrupted time to finish a watch. The watches Hora handled were no less complex than those of Tempus, but he had designed them so that he could put together sub-assemblies of about ten elements each. Ten of these subassemblies, again, could be put together into a larger subassembly and a system of ten of the latter constituted the whole watch. Hence, when Hora had to put down a partly assembled watch in order to answer the phone, he lost only a small part of his work, and he assembled his watches in only a fraction of the man-hours it took Tempus.”

- To manage variety. Generation of diversity can be achieved by declining a platform. Such a possibility of late differentiation is crucial in a sector in which the high fixed costs combined with regulated prices limit profitability.

3.2 The case of GEV

It makes sense to think of the development of a GEV as a modular system, since it is possible to decompose it between three broad subparts that are all necessary (despite not with the same importance) but can be developed almost independently one of each others. The three subparts that compose GEV are antigen, vector and adjuvant.

First of all, to develop a vaccine firms need an antigen, which is the substance that stimulates the immune response, i.e. the production of antibodies. Since antigens mark foreign agents in the organism, they are central to trigger immune response. It is only the reconnaissance of the antigen by immunocompetent cells that active the immune reaction. Antigens can be classified according to their origins: exogenous if they have entered the body from the outside, for example by inhalation, ingestion, or injection, or endogenous if they have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. Specialists usually agree that the identification and production of antigens is the most important stage for vaccine production.

Having identified an antigen to provoke an immune response against a given disease is not enough to produce a GEV. To produce the antigen you also need to be able to carry the naked GEV that will code for this antigen within the human cells. This requires the use of sophisticated transfection techniques in order to pass the frontiers of the cell that were described above (to enter the cell, to enter the nucleus, etc.). Transfection typically involves opening transient holes in cells to allow the entry of extra-cellular molecules. Transfection differs from transformation since the DNA is not generally incorporated into the cells genome but is only transiently expressed¹⁰. Since the DNA introduced in the transfection process is usually not inserted into the nuclear genome the foreign DNA is lost when the cells undergo mitosis. Notice that there are various methods of introducing foreign DNA into a cell: Electroporation, heat shock, gene gun¹¹ or the use of viruses as carriers¹².

Research on transfection can be connected to research on the galenic aspects of the medicine. Techniques of transfection like those described above changes the route of delivery of vaccines, usually based on injections. Most techniques of transfection rather use more complex delivery systems¹³. Yet, those new techniques to deliver the vaccine into the cells, although quite efficient, may somehow be considered as too complex to be used widely.

¹⁰ This distinction is central. Nowadays, transfection is allowed but transformation is not for ethical and safety reasons.

¹¹ The gene gun technique consists of coupling DNA to a nanoparticle of an inert solid which is then shot directly into the target cell's nucleus (nanotechnology drug delivery systems).

¹² All viruses introduce their genetic material, which contains instructions of how to produce more copies of the virus, into the host cell. The host cell then carries out these instructions and produce additional copies of virus. Viruses can therefore be used as vehicles to carry good genes into a human cell. To do this we need to remove the genes in the virus that cause disease and to replace them by genes encoding the desired effect (the production of antigens in the case of vaccines).

¹³ For instance, the PowderJect's delivery technology works by the acceleration of fine particles to supersonic speed within a helium gas jet. This system provides effective delivery of vaccines, without the pain or the use of needles (Powderject, is a drug and vaccine delivery company specializing in the needleless injection of drugs. It has been bought-out by Chiron in 2004, which was in turn absorbed by Novartis in 2005).

Sometimes less efficient but simpler techniques may be preferred, especially in countries where the workforce is not well trained (in developing countries, for instance). It is indeed important to develop systems that can be manipulated by local health workers. Hence, simple delivery systems as oral or mucosal ones will be better accepted by patients.

Placing the DNA coding for the desired antigens into a vector that delivers it into the cells is enough to produce a vaccine but the efficacy of this vaccine can still be improved by using products that enhance the immune response. Those products are called adjuvant or more broadly enhancing technologies. Adjuvant can be defined as agents that modify the effect of other agents while having few if any direct effects when given by themselves. Specifically, in immunology an adjuvant is an agent which, while not having any specific antigenic effect in itself, may stimulate, activate or modulate the immune system, increasing the response to a vaccine¹⁴. In short, an adjuvant is a substance designed to boost the vaccine's protective effect.

With respect to the development of GEV one could therefore write the following simple equation:

$$\text{GEV} = \text{one antigen} + \text{one vector} + \text{one adjuvant}$$

The development of GEV requires combining three elements. Yet, to consider it as being a modular system, too properties must still be satisfied: First, the subparts that compose GEV must be autonomous, i.e. can be considered independently one of each other. Second, those modules can be changed or recomposed in different ways in order to produce different products. The development of GEV fulfils those two properties, at least in part.

First, the three modules that compose GEV can be produced in a relatively autonomous way. Firms involved in the production of vectors, antigens or adjuvants can remain independent one from each other, at least during the first stages of the research. Until a certain point, the production of vectors, for instance, can be undertaken without any consideration for the antigen or the adjuvant. Yet, the three modules cannot be considered as perfectly independent. The conception of a module cannot be completely disconnected from other modules. The method used for transfection for instance (the vector) is never completely neutral. It always affects the efficacy of the antigen.

The second property of a modular system is also partly satisfied in the case of GEV since it is possible to combine the modules in various ways, at least in theory. Broadly speaking a vector can serve for many antigens and one antigen can be carried out by many vectors. Similarly, one adjuvant may enhance the performance of several different antigens. The combinations among the modules may therefore lead to many new possibilities. Yet, again in practice this modular property is coming up against the fact that modules are not perfectly independent. Each module needs specific adjustments before being combined with another one.

4. Patents in the development of GEV: a tool of co-opetition

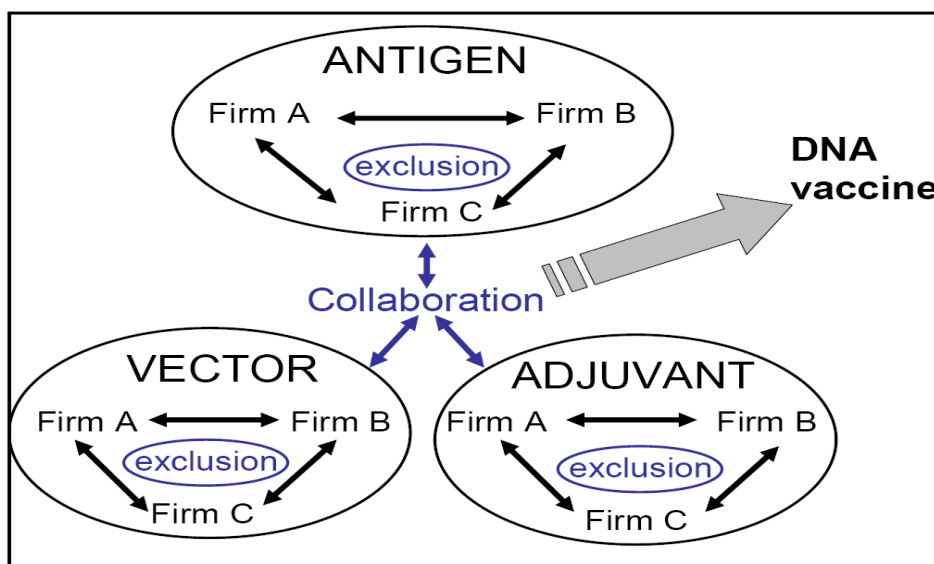
Despite the dampers raised in the former part, we think it as promising to describe the production of GEV as a modular process. This modular aspect may trigger a peculiar

¹⁴ For instance aluminum salts are used in some human vaccines (Baylor, Egan and Richman, 2002).

industrial structure with respect to the production of GEV. Players are usually specialised in one specific module and few firms are able to manage the three modules, which means that few firms are able to develop a GEV in an integrated way. Collaborations among firms are therefore inevitable. This modular structure, which allows the autonomous production of each element of a GEV independently of other modules, raises the question of the interaction between the different modules. How players combine to arrive to produce a vaccine? Which kinds of arrangements are implemented?

We are specifically interested in this paper in the role of patents to ensure the coordination among the different modules. Our claim is that patents play a central role in the production of GEV. It is the patent system that enables the existence and the interaction of the different modules. Yet this role is very different than the traditional vision of patents, which considers the latter as being merely devices that increase incentives to do research. Rather, here patents play clearly also a role of coordination. They are structuring elements in the production of GEV. Each element in a specific module can indeed be patented, which both increases the incentives to invest in a given module and enable the interaction among modules. In short, without patents modules would not exist (firms would have no incentives to invest in a given module) and the interaction among modules would be more difficult. The role of the patent system is therefore two-fold: on the one hand patents are used as tools of exclusion within each module and on the other hand they are used as instruments of coordination among the different modules as illustrated in figure 1 below.

Figure 1: Co-opetition in the development of GEV



4.1 Patents to exclude competitors within modules

First, patents are a tool of competition within each module in which firms are rivals. Inside modules we can therefore observe a traditional use of patents as tools of exclusion and protection against imitators. Firms involved in vector production, for instance, usually do not collaborate with other firms producing vectors. They rather use their patent portfolios to exclude other vector producers from imitating them so that they enjoy a monopoly position on their productions. Our interviews with many actors in the field confirm that without patents

most firms would not invest in R&D¹⁵. Indeed, in life science it is well-known that patents are highly important to appropriate the returns of an innovation and to enhance incentives to do research (Levin *et al.*, 1987; Cohen *et al.*, 2000). Firms acting specifically in biotechnologies are small firms faced with high competitive pressures and thus they strongly rely on patents because they usually do not have any other tangible asset. Patents are the only element to valorise in front of potential partners and financiers. Furthermore, patents are also central due to the codified nature of the underlying knowledge. Conversely to other sectors, firms in life science can be imitated relatively easily, which decreases their incentives to invest in R&D. In short, within each module firms are rivals and tend to use patents as a tool of protection against competitors, as described by the traditional Arrowian vision of patents.

Two important remarks may nevertheless put into perspective this traditional view of patents as devices to exclude: First, vaccine development does not involve only codified knowledge. Vaccines are far from corresponding to the traditional chemical paradigm that occurs in the pharmaceutical industry. To develop a vaccine firms must also possess the know-how to consistently produce a safe and effective biological product. Hence a vaccine cannot be as easily imitated as a chemical component¹⁶. This dependence on know-how, which is of course not covered by patents, may attenuate the role of patents as being essentially a device to exclude. Firms in vaccine may not need patents to exclude since they are already protected by their know-how.

Second, it comes out of our interviews that the peculiar current situation of the overall sector implies that firms within modules are not completely rivals but also allies in some sense. Interest of firms may converge in the sense that as soon as one firm will commercialise a product it will benefit to the whole industry, including competitors, and not only to the innovative firm. This positive spillover is explained by the current financial situation of the industry. According to many players the main concern today is to find financing¹⁷. Financiers are more and more reluctant to fund R&D, since the biotech revolution has started almost 20 years ago and there is still no return over the investment. Yet, most players are convinced that new therapeutic products will emerge soon, so that their main objective is to keep being financed until this happens. Once a firm will succeed, it is likely that this will attract again the financiers and that this will benefit the whole sector. In short, this situation may induce some collaborative behaviour and mitigate the effect of competition within modules.

However, those two features may introduce some collaboration but overall they do not counterbalance the competitive situation within modules in which patents are mostly used as

¹⁵ Our interviews, if they tend to show that patents are essential to ensure industrial investments in the field of GEV, also reveal an interesting feature. Patents seem to be so deeply rooted in the mind of the players that the latter can hardly think about a situation without patents. When asked whether they would continue to invest in R&D if the patent system did not exist, firms rarely imagine a fictive situation in which nobody would have a patent but rather they usually consider a situation in which they would not have a patent but the other firms would. Therefore they almost always answer “without patents we would stop investing”. This difficulty for firms to imagine a world without patents may induce a bias in their answers.

¹⁶ This dimension of vaccine also implies that imitators of a vaccine must pass through clinical trials like the innovator. They cannot proceed like generic producers in the chemical-pharmaceutical paradigm. This also increases firms' incentives to innovate even without patents.

¹⁷ Yet, it seems that concerning GEV in particular firms can still find financing relatively easily. Almost all our interviews confirm that public funding is present and that venture capital funds can be mobilised although most firms also complain that the latter intervene too late in the innovation process (definitely not earlier than clinical trials phase 2), thus not assuming the risk inherent to early stages of innovation.

tool of exclusion. Without the protection offered by patents it is doubtful that firms would engage into costly and uncertain investments to produce GEV.

4.2 Patents to ensure coordination among modules

Completely different is the situation among the different modules. Here firms are not rivals but clearly allies that must collaborate to achieve a common goal. Firms in different modules must combine their competences in order to produce a vaccine. Those interactions among firms in separate modules are facilitated by the existence of the patent system. In this sense patents are clearly also tools of collaboration. They facilitate interactions among the elements from different modules because they both disclose and protect the knowledge. As it has been showed in former studies, it is the coupling of two properties – disclosure of the knowledge underlying the invention and protection of this knowledge- that makes patents central elements to ensure coordination within an industry. Patents can help the interactions among modules at two different levels:

- (i) They signal the competences of the actors of the innovation process.
- (ii) They enable technology trading, through licensing agreements for instance, and they are central to frame inter-firms collaboration.

(i) Patents signal where competences are located. When an innovator applies for a patent he must provide a description of the innovation, which must enable its reproduction by any person knowing the “state of the art”. Eighteen months after the application this description is published, i.e. becomes public, even if the patent is not granted. The patent system contributes therefore to the creation of a database that contains most of the technological competences in a wide area of technological fields. Yet, beyond the technical information they include, patent databases also provide information about who does what, about the actors present in the field. This information concerning the “know-who” (Lundvall and Johnson, 1994) is often essential to find partners or to avoid entering technological fields that are already explored by competitors.

In this sense, for a firm a patent may also be a way to increase its reputation and to indicate to the scientific and industrial communities that the firm is present and competent in a given field. With respect to GEV, patents enable therefore firms to establish contacts in a field in which the multiplicity of small and heterogeneous actors may complicate the identification of partners. As argued by Mazzoleni and Nelson (1998), patents are advertising support. This signalling dimension of patents enables patentees to find partners with whom to collaborate, to collect funds or to hire bright students more easily (Pénin, 2005). In the development of GEV, patents may therefore facilitate the contacts among actors in different modules. For instance, firms specialised in the production of antigens and looking for partners specialised in vectors can scan patent databases in order to find collaboration. Yet, it must be acknowledged that this signalling role is not specific to patents. It can also be fulfilled (maybe even more effectively) by publications databases, conferences, informal relationships, etc.

(ii) Beyond this dimension of “knowledge signalling” patents are central to frame the modular process in DNA vaccines essentially because they facilitate technology trading and inter-firms collaboration. We will see that it is the coupling of the properties of disclosure and protection offered by patents that makes them so useful to structure interactions among firms. In this sense patents enable firms to specialise in a single module, since they make it possible to valorise independently the production in a given module and then to collaborate and trade with actors in other modules.

First, patents help technology and knowledge trading. Firms specialized in a given module can produce knowledge, patent their results and then sell them through licensing contracts that specify the price and the terms of the transaction. Such exchanges could hardly emerge without the existence of the patent system since only the combination of the two properties of disclosure and protection makes it possible. Patents both signal where competences are located and protect those competences, thus preventing free riding from occurring. Therefore, paradoxically, property rights may often favour knowledge transfer. In a sense, the patent system allows the creation of a market for technologies and highly codified knowledge¹⁸. Yet, patents may also sometimes allow the transfer of the tacit component of technologies by including in licensing contracts clauses of assistance, of exchange of employees, etc. For instance, Foray (2004, p. 136) wrote: “Patents create transferable rights and can therefore help to structure a complex transaction that also concerns unpatented knowledge”.

Here, the coupling of the elements of exclusivity and revealing inherent to a patent are essential with respect to the implementation of a market for technologies. The coupling of these two properties of disclosure and protection allows in some sense resolving the Arrow’s paradox (1962)¹⁹. It enables innovators to sell their innovation with the peace of mind that no entity will “hijack” it. In clear, the patent system allows the separation of inventors and exploiters of an innovation in a particular modules allowing for gains in specialisation by the respective entities. In this context, the inexistence of patents would mean that the same entity would have to be both the exploiter and inventor.

In the case of GEV, this role of patents seems to be essential. We indeed observe many patent licensing among firms from different modules. Our interviews all confirm this feature and the fact that firms from different modules may put their competences in common through patent licensing.

Second, beyond facilitating technology trading through licensing, patents also ease more integrated inter-firms collaborations such as research joint venture. Indeed, R&D cooperation is a risky process in the sense that participants must often share parts of their most important intellectual assets. Since patents protect the knowledge held by a firm from plundering by her partners, they decrease the risk of opportunistic behaviours and of hold up of competences. It follows that firms protected by patents may be more willing to be involved in R&D cooperation (Ordovery, 1991). Patents are also useful bargaining devices to set up the terms of the interaction. They enable to assess the competences of each partner, i.e. they provide a benchmark that allows firms to compare their relative competences. Moreover, as they represent a credible threat to block the entente, they limit the effect of size or financial asymmetries. Finally, patents facilitate the coordination between sometimes very heterogeneous actors because they represent a common language that can be understood by all of them (public labs, big multinationals, consulting agencies, financing organisations, etc).

¹⁸ Empirical evidence of such markets for technology exists in chemicals (Arora and Fosfuri, 2000), semiconductor, biotechnologies or electronics (Arora, Fosfuri and Gambardella, 2000).

¹⁹ Arrow (1962) explains why it would be hard to implement a market to trade information. He points out that if the seller does not disclose the information then no buyer will ever want to buy it since they do not know the value of it. But once it is disclosed then the buyer has acquired it at no cost. A famous illustration of this problem is given by Tirole (2003, p. 23) who tells us the story of Robert Kearns, the inventor of the windshield wiper. Having no possibilities to commercialise alone his invention Robert Kearns proposed a collaboration to Ford, to which he disclosed the idea and some of the technical aspects. Ford refused the collaboration and some time later introduced on the market a similar product with only slight technological differences.

Our interviews confirm this view of patents as facilitating inter-firms collaboration. For instance, we interviewed a firm involved in the development and commercialisation of chemical based vectors that serve to transfer genes or other bio-molecules (proteins for instance) within cells in-vivo or in-vitro (viruses are usually used for this transfer). This firm is currently engaged in an important project of vaccine against bladder cancer with US partners. However, it acknowledged that without patents this collaboration would hardly be possible.

In conclusion, we suggested here that patents are structuring elements in the production of GEV since they ease the coordination among the different modules needed to develop a vaccine. We showed that the patent system allows a division of labour and gains of specialisation in the development of GEV. In some sense, the patent system provides an adequate interface among the different modules.

4.3 A tragedy of the anticommons?

This role of patents as inducing a new division of labour was already emphasised during the biotech revolution at the end of the last century. The emergence of biotech led to a new organisation in drug production, which adopted a two-stage process involving first the research and development and then the trials and marketing. Instead of an integrated production in which big pharmaceutical companies were screening new compounds, testing and commercialising them, the biotech revolution has led to a division of labour between the research of new active compounds on the one hand and the testing and commercialising of those compounds on the other hand. Based on scientific excellence new biotech firms discovers new compounds, apply for patents and then license and sell them to big pharmaceutical companies, which have the ability (financial and organisational) to test and commercialise the drug on a marketplace, thereby earning some revenue.

The role of the patent system is obvious in this process. Big pharmaceutical companies are the only actors to generate revenue from the market place. Without patent protection new biotech firms would never engage into costly research, which means that big pharmaceutical companies would have to undertake those researches by themselves, which would be more costly than to buy licence to new biotech firms. Patents here allow a division of labour enabling each actors of the innovation process to concentrate on the aspect in which it is the most efficient. They are the interface between new biotech firms and big-pharmaceutical companies.

Within the development of GEV, the division of labour is still push forward in the sense that patents enable not only to distinguish between the research stage and the development and commercialisation stage but also to specialise during the research stage. New biotech firms are leading complementary research on different modules and then sell their research to firms that will have to develop and produce the finite vaccine. Firms that ensure the commercialisation of the vaccine do not have to interact with only one research company but with several start-ups, each of them specialised in one single module.

Yet, this modular structure may encounter one important problem. We are indeed here in the exact configuration described by Cournot in its seminal work in 1838 about the properties of

models dealing with complementary intermediate goods²⁰. Cournot demonstrated what is nowadays called the “tragedy of the anticommons” (Heller and Eisenberg, 1998), an expression that relies on the notion of “tragedy of the commons” stressed by Hardin (1968). As stated by this biologist, the lack of property rights on a common good can lead, if the good is used above its regenerative capacities, to its entire destruction. The idea of the anti-common tragedy fosters on the exact reverse problem. In the case of complementary goods there is a risk of suboptimal use of resources linked to the addition of monopoly situations that may lead to an overall price too high in order to exploit the resource. A tragedy of the anti-commons therefore means that a good is under-exploited due to a price too high induced by the addition of monopoly positions on intermediate modules. With respect to the case of GEV, the addition of monopoly position on each module that composes a vaccine may sharply increase the overall price of production of the vaccine and at the end, may jeopardize its production. It is therefore in the interest of society that policy makers watch this situation and, if necessary, try to improve the interactions among modules in order to decrease the price of producing the vaccine.

5. Conclusion: Rethinking the role of patents

This paper explored the role of patents in the development of GEV. We shifted from a traditional vision of patents - as being merely institutional devices that provides incentives to invest in GEV- to a vision that considers patents as structuring elements of collective innovations. Indeed, we showed that the production of GEV adopts a modular structure, i.e. the development of a vaccine is achieved through the interaction of several sub-products or modules. To bring a vaccine on the market a firm must combine one element from different modules. Then we showed how patents can facilitate the interactions between the different modules. We argued that patents in some sense ensure the interface among the different modules. Therefore we developed a vision of patents as being tools of co-opetition rather than solely tools of competition. Firms involve in GEV use patents both to exclude and to collaborate. They aim at excluding competitors within their own modules and they aim at collaborating with complementors in other modules.

This view of patents as being not only devices to increase incentives to invest in R&D but also instruments that ease the coordination of the innovation process is in line with the recent works of Bureth *et al.* (2005) and Cohendet *et al.* (2006). The latter deepened the work of Winter (1993) and Callon (1993 ; 1999) on the properties of knowledge in an emerging situation. They show that the arrovia model is simplistic in the sense that it addresses only stable and mature situation in which actors and technologies are well defined. In order to underline the dilemma between incentives and diffusion, Arrow simplified the innovation process to a two phase process: invention and then diffusion of this invention. All the aspects related to the complex dynamics linked to the genesis of the innovation were neglected thus reducing innovation to a static two step game.

Formatted: English (U.K.)

Yet, during the first step of the creation of technological trajectories, the traditional arrovia framework does not apply. It underestimates the need for common knowledge between actors. Callon (1999) shows clearly that during the first phase of the creation of an innovation, when

²⁰ Cournot shows that, contrary to what was argued by traditional economic theory, sometimes one unique supplier (that has a monopoly position) is better for the overall social surplus than an addition of several independent suppliers. He showed that in the case of complementary intermediate goods one unique supplier for all the intermediate goods is better than one monopoly supplier for each intermediate good.

common language and schemes do not yet exist, it is the exact opposite situation of the one described by Arrow that happens. Knowledge in this context is marked by strong rivalry (it is hard to reproduce it outside the local context where the discovery has been made) and strong exclusivity (the invention is linked to the tacit knowledge of the inventor), so the risks are high for a lack of common cognitive grounds to break into this process. In terms of risks for the innovator, it is therefore less likely that diversion might occur than for him not to be understood. It is necessary during the first stages of technological trajectory construction for actors to cooperate, and above all to converge on shared objectives. Technological trajectories cannot develop by themselves unless public or semi-public common knowledge ground is defined and created, that will enable the reproduction, enlargement, and development of the first creative ideas.

Hence, the first stages of innovation development are a complex and mostly collective process during which agents need to exchange and cooperate. The way patents are used by the actors of this process may therefore be quite different than suggested by the traditional model. Instead of being aimed at excluding competitors patents may be used in order to ease inter-firms interactions and collaboration.

This is exactly what has been shown in this paper but for another reason than the emerging nature of the industry. We considered a case of modular innovation, i.e. an innovation that requires the assemblage of several sub-components. The properties of this kind of complex innovations (by opposition to discrete innovations such as pharmaceutical drugs) are well known and have been studied in the case of electronics. Most scholars have raised similar results than ours in this industry by showing that firms usually gather huge patents portfolios not in order to exclude potential competitors but in order to deal and to trade those patents with other firms so that they keep the freedom to use specific innovations (Grindley and Teece, 1997; Attia, Davy and Rizoulières, 2000; Hall and Ziedonis, 2001). Although we did not observe exactly the same thing, the philosophy underlying the use of patents in the development of GEV is similar in the sense that firms may use the patent system in order to ease exchange between modules.

To push forward the comparison it must be noted that Corbel (2003) also mentions a use of patents as a tool of co-opetition in the case of electronics. Yet the example of Corbel is slightly different than ours. He shows that in electronics firms use their patents portfolios in order to collaborate with other firms that have gathered important patents. Firms with important patent portfolios exchange their patents in order to access technology protected by patents held by competitors. Yet, those patents portfolios also serve to exclude those firms that do not have important patents. This use of patents may therefore trigger inertia in the industry, protecting incumbents and preventing new firms to enter the game.

In conclusion, we proposed here a view of patents that is more realistic than both the traditional view focused only on exclusion and the pro-patent view that tends to reject all the criticism on patents. We argued, in line with the pro-patent view, that patents can indeed be structuring elements of the innovation process and that in this sense they are useful and necessary for innovation to occur, but we also stressed the risks that may be induced by patents in such situations of modular innovations. Patents may block the innovation process by augmenting the overall price to exploit the innovation. Furthermore, patents may create entry barriers that may induce a decline of the innovation rate. Although we have showed that patents are usually good for social welfare, we also see that there is nevertheless many

reasons for policy makers to remain cautious and to correct the abuses induced by inappropriate patent uses.

To be used in section 5

“While new technologies are our best hope in the long run, new technologies may exacerbate supply shortage in the short run, by undermining incentives to invest in older plants that are destined to become obsolete” (Danzon et al., 2005, p716). By accelerating the pace of innovation, modularity might help to reduce the period of transition from one vaccinal paradigm to the other.

Modularity helps to develop vaccines with a strong technological content. It allows a clear diversification of the products, but induces also a strong increase in prices. It raises several questions, related to the supply oriented towards the poorer nations. Can the new vaccines finance (directly, or indirectly, under which regulation mechanisms) more traditional vaccines. To the same extent, will modularity facilitate technological transfers toward pharmaceutical industry in under-developed countries. In that case, does it mean that the barriers to generic entry, still existing on the vaccine market, would fall (modification of the business model adopted by the big five producers)

References

- Arora A., Fosfuri A. (2000), « The Market for Technology in the Chemical Industry: Causes and Consequences », *Revue d'Economie Industrielle*, vol. 92, pp. 317-334.
- Arora A., Fosfuri A., Gambardella A. (2000), « Markets for Technology and their Implications for Corporate Strategy », working paper Yale School of Management, 39p.
- Arrow, K. J., 1962, « Economic Welfare and the Allocation of Resources for Invention », dans *The Rate and Direction of Inventive Activity: Economic and Social Factors*, Princeton university Press, pp. 609-625.
- Arundel A., van de Paal G. (1995), « Innovation strategies of Europe's Largest Industrial Firms », unpublished manuscript, MERIT.
- Attia R., Davy I., Rizoulières R. (2000), « Innovative Labor and Intellectual Property Market in the Semi-Conductor Industry », dans *Technology and Markets for Knowledge*, Kluwer Academic Publishers.
- Baylor, Egan and Richman (2002), “Aluminum salts in vaccines--US perspective”, *Vaccine*, vol. 20, pp. S18-23
- Bureth A., Levy R., Pénin J. et Wolff S. (2005), « Strategic Reasons for Patenting : Between Exclusion and coordination Rationales », *Rivista di Politica Economica*, pp. 19-46
- Callon M. (1999), « Le Réseau comme Forme Emergente et comme Modalité de Coordination : le Cas des Interactions Stratégiques entre Firmes Industrielles et Laboratoires Académiques », dans Callon et al., *Réseau et Coordination*, Economica.
- Callon M. (1993), “Is Science a Public Good?”, Fifth Mullins Lecture, Virginia Polytechnic Institute, March 23, 1993.
- Cohen W. M., Nelson R. R., Walsh J. (2000), « Protecting their Intellectual Assets: Appropriability Conditions and Why US Manufacturing Firms Patent (or not) », NBER working paper 7552.

- Cohendet P., Farcot M. and Pénin J. (2006), "Entre incitation et coordination : Repenser le rôle du brevet d'invention dans une économie fondée sur la connaissance", *Management International*, vol. 10.
- Corbel P. (2003), « Le brevet : un outil de coopération/exclusion », cahiers de recherche du Larequoi 2003/1, pp. 30-44.
- Daar A.S., Martin D.K., Nast S., Smith A.C., Singer P.A., Thorsteinsdottir H. (2002), "Top 10 Biotechnologies for improving global health in developing countries", University of Toronto, Joint Center for Bioethics, available from www.utoronto.ca/jch/research/documents/top10ng.pdf
- Danzon P.M., Sousa Pereira N., Tejwani S.S. (2005), "Vaccine supply : a cross-national perspective", *Health Affairs*, vol. 24, n° 3, pp. 708-717.
- Ford G. M. (2005), "Rapid-response vaccines – does DNA offer a solution?", *Nature Biotechnology*, vol. 23, n°9, September, pp. 1059-62.
- Goto A., Nagata A. (1996), « Technological Opportunities and Appropriability », NISTEP report n°48, Tokyo.
- Grindley P., Teece D. (1997), « Managing Intellectual Capital: Licensing and Cross-Licensing in semi-conductors and electronics », *California Management Review*, vol. 39, pp. 8-41.
- Hall B. H., Ziedonis R. H. (2001), « The Patent Paradox Revisited: an Empirical Study of Patenting in the US Semiconductor industry, 1979-1995 », *Rand Journal of Economics*, vol. 32, pp. 101-128.
- Hardin G. (1968), « The Tragedy of the Commons », *Science*, vol. 162, pp. 243-1248.
- Heller M. A., Eisenberg R. S. (1998), « Can Patents Deter Innovation? The Anticommons in Biomedical Research », *Science*, vol. 280, pp. 698-701.
- Jaffe A. (2000), « The US Patent System in Transition: Policy Innovation and the Innovation Process », *Research Policy*, vol. 29, pp. 531-557.
- Kortum S., Lerner J. (1999), « What is Behind the Recent Surge in Patenting? », *Research Policy*, vol. 28, pp. 1-22.
- Levin R.C., Klevorick K., Nelson R.R., Winter S. (1987), « Appropriating the Returns from Industrial Research and Development », *Brooking Papers on Economic Activity*, vol. 3, pp. 783-820.
- Lundvall B. A., Johnson B. (1994), "The Learning Economy", *Journal of Industry Studies*, vol. 1, pp. 23-42.
- Mansfield E., Schwartz M., Wagner S. (1981), « Imitation Costs and Patents : An Empirical Study », *The Economic Journal*, vol. 91, pp. 907-918.
- Mazzoleni R., Nelson R.R. (1998), « The Benefits and Costs of Strong Patent Protection : A Contribution to the Current Debate », *Research Policy*, vol. 27, pp. 273-284.
- Ordover J. A. (1991), « A Patent System for Both Diffusion and Exclusion », *Journal of Economic Perspectives*, vol. 5, pp. 43-60.
- Pasternak A., Sabow A., Chadwick-Jones A. (2006), "Vaccines: market on the rebound", *Pharmaceutical Executive*, may 2006, pp. 110-120.
- Pénin J. (2005), « Open knowledge disclosure, incomplete information and collective innovations », document de travail BETA 2005-10.
- Sakakibara M. - Branstetter L. (2001), "Do stronger patents induce more innovation? Evidence from the 1988 Japanese patent law reforms", *Rand Journal of Economics*, vol. 32.
- Scherer F.M., Herzstein S.E., Dreyfoos A.W., Whitney W.G., Achmann O.J., Pesek C.P., Scott C.J., Kelly T.G., Galvin J.J. (1959), *Patents and the Corporation: A Report on Industrial Technology Under Changing Public Policy*, Harvard University.
- Taylor C. T., Silberston Z. A. (1973), *The Economic Impact of the Patent System: A Study of*

- the British Experience, Cambridge University Press.
- Tirole, J., 2003, Protection de la Propriété Intellectuelle: Une Introduction et Quelques Pistes de Réflexion, in Propriété Intellectuelle, report n° 41 of the Conseil d'Analyse Economique, La documentation Française.
- Vignier P. (2002), La France dans l'économie du savoir: pour une dynamique collective, report Commissariat Général au Plan, La Documentation Française.
- Winter S. G. (1993), « Patents and Welfare in an Evolutionary Model », Industrial and Corporate Change, vol. 2, pp. 211-231.