A RESEARCH AND DEVELOPMENT CASE IN THE BIOTECHNOLOGY FIELD: CELL THERAPY

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I. Introduction

With the development of governmental policies to control escalation of health care expenditures, as well as public opinions' growing concerns about iatrogenic risks of medical procedures, which have been recently exemplified by the political scandals in various countries that followed massive HIV contamination of haemophiliacs through blood products in the 80's, the question has been often raised that more and more stringent regulations may have strong counter-productive effects on the rate of medical innovation (1). Some economic researchers and most industry representatives have regularly underscored that, in relation with evolution of pre-market approval regulations, the risks for pharmaceutical R&D have increased and may constitute impediments to drug innovations in the long run. Barriers to innovations may even be stronger for new types of products facing major uncertainties from both technical and regulatory points of view, as it is the case for therapeutic use of biological products from human origin.

In recent years, new technologies such as somatic cell and gene therapies have moved from the bench to clinical evaluation with considerable speed and they have focused a lot of industry's interest. Somatic cell therapy can be defined as the administration to humans of autologous, allogeneic or xenogeneic living somatic cells that have been manipulated or processed to change their biologic characteristics with a therapeutic purpose. The administration of cells that have undergone ex vivo genetic manipulation builds a technical bridge between somatic cell and gene therapies. In the States, it has been shown that these therapies and the cellular products they used could meet various statutory definitions and therefore were potentially subject to different laws and regulations (2). In France, since 1994, there has been a heated legislative debate and endless battles between administrative bodies to determine what should be the regulatory status of therapeutic cell products and if they should either be assimilated to drugs or blood products or even organ transplantations (3). Industrial economics have showed that firms tend to be drawing heavily on experience from the use and commercialisation of past related medical technologies in order to anticipate future prospects of innovations like cell or gene therapies, and may be specially sensitive to regulatory uncertainties in this field.

Using the case of somatic-cell therapies in the French context, we would try to contribute to the debate about optimal regulation of these new types of medical innovations. A first approach was an empirical analysis of the various strategies of the actors involved in such

technical innovation in order to identify what are the most important issues at stake for regulation and the various strategic behaviours of the agents involved. A second approach was to confront these empirical observations with a normative analysis based on the application of bargaining theory to discuss the conditions, the modalities and the rhythm of the introduction of new regulation for biotechnological innovations.

II. Cell therapy: a case of innovation

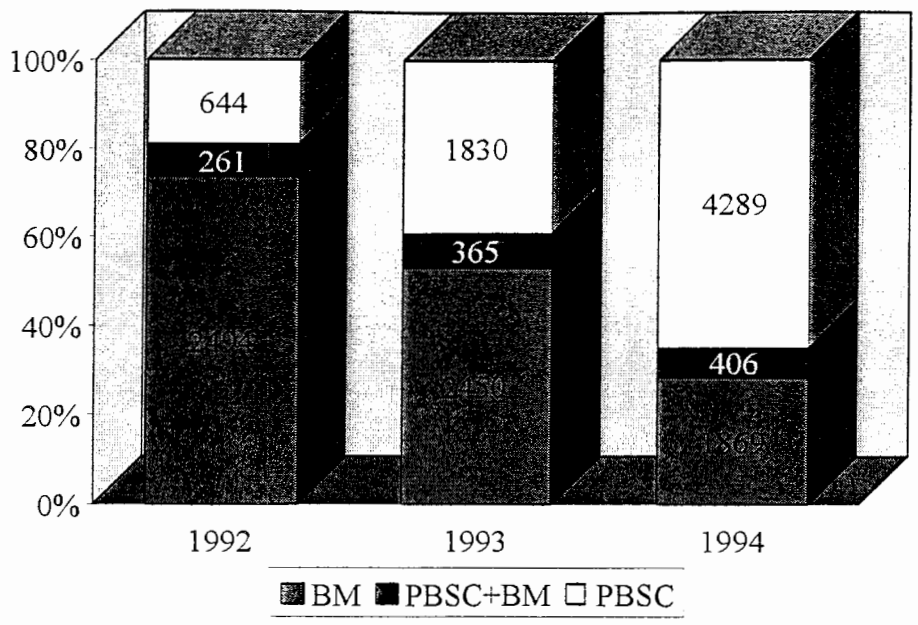
1. From bone marrow transplantation to peripheral blood progenitor cell transplantation

It has been recognised long ago that treatment of cancers, which often includes chemotherapy or radiation therapy to eliminate the diseased cells, frequently destroys a portion or all of the stem cells[1] and dividing progenitor cells in the bone marrow. Such, damage to the stem cells, which are responsible for the renewal process, is invariably fatal if they are not replaced. The purpose of transplantation is to replace these damaged cells with healthy marrow. It is now established that high-dose chemotherapy followed by bone marrow transplantation (BMT) can be an effective therapeutic method in the management of some malignancies (4, 5). These techniques include autologous transplantation (where the patient's own bone marrow is collected, stored and then reinfused into the patient after treatment with high doses of chemotherapy and/or radiotherapy) or an allogeneic one (where a healthy donor's bone marrow is collected and reinfused into the patient).

It was also known since a long time that hematopoietic progenitor cells reside not only in the bone marrow but also circulate in the peripheral blood of mice and man. Recently, it has been discovered that chemotherapy and haematopoietic growth factors such as G-CSF or GM-CSF, alone or in combination with cytotoxic drugs, greatly increase the numbers of circulating peripheral blood progenitor cells (PBPC) (6). Therefore, it became possible and feasible to collect hematopoietic stem cells directly from the peripheral blood of patients rather than from bone marrow harvest. With this technical possibility of collecting PBPC, a very rapid substitution of PBPC collection rather than BM harvest for autotransplantation, as supportive care for cancer therapies, has occurred. As figure 1 shows in the case of Europe, transplantation of mobilised PBPC became very quickly a widely used alternative to autologous bone marrow transplantation.

[1] A stem cell is, by definition, a cell which is still able to divide without differentiating, and therefore retains the potential to ultimately differentiate into all elements of the bone marrow (mainly, white cells, platelets and red cells).

Figure 1 : Evolution of autologous stem cells transplantations in Europe (1992-1994)



Various arguments were used in favour of this substitution since the early stage of development of the new technology. These included an easier collection of blood-derived hematopoietic progenitors without the use of general anaesthesia. In a survey aiming to compare anxiety, pain and discomfort of 65 cancer patients submitted to either PBPC collection or bone marrow harvest, we showed that PBPC patients experienced significantly less anxiety and pain than BM patients (7).

The first clinical trials in the autologous case showed that PBPC transplantation offered a number of advantages over BM transplantation, especially a more rapid hematopoietic recovery after marrow-ablative therapy with the potential for reduced tumor cell contamination and a decrease of the procedure's cost (8). These results are just confirmed by the first randomised control studies comparing BM autotransplantation and PBPC autotransplantation (9, 10). In one of these trials concerning 129 adults and children with non-Leukaemic malignant disease which was recently carried out in France (9) we were able to introduce a detailed economic evaluation (table 1) which confirmed that cost-minimisation arguments can be added to clinical ones in favour of substitution of autologous PBPC transplantation to autologous BM transplantation (11).

Table 1: Comparison of the mean total cost per patient for two therapeutic strategies (PBPC autotransplantation and BM autotransplantation) for adults (n=81) and children (n=48) with non-leukaemic malignant disease

	Adults				Children			
	PBPC		BM		PBPC		BM	
Room cost	58 750	(45%)	66 933	(43%)	64 147	(50%)	95 290	(52%)
Transfusions	16 182	(12%)	31 715	(20%)	15 363	(12%)	26 314	(14%)
Anti-infectious	9 673	(7%)	11 119	(7%)	12 724	(10%)	13 796	(8%)
Conditioning regimen	4 820	(4%)	4 303	(3%)	2 628	(2%)	2 689	(1%)
Laboratory tests	7 591	(6%)	9 322	(6%)	7 782	(6%)	12 018	(7%)
Post-transplant G-CSF	9 696	(7%)	14 354	(9%)	8 869	(7%)	13 253	(7%)
Harvest	23 039	(18%)	18 612	(12%)	17 945	(14%)	18 612	(10%)
Mean total cost	**129 751**		**156 358**		**129 458**		**181 972**	

#All costs are mean costs, in 1995 French Francs
Le Corroller et al., *Pharmacoeconomics*, 1997

Similar preliminary results – a more rapid hematopoietic recovery and a decrease of the procedure's cost–have also been found in the allogeneic case (5, 12). A randomised trial comparing allogeneic blood stem cell transplantation after priming with G-CSF to allogeneic bone marrow transplantation and including an economic evaluation is currently going on in France.

2. A perturbing innovation

The substitution of PBPC to BM transplantation in cancer care could have been the object of the « classical » debates around the rapid diffusion of any medical innovation, which usually concerns its appropriate indications, the scope of that diffusion and its evaluation on cost-effectiveness grounds. It has however created even more controversies because PBPC is emblematic of a totally new class of therapeutic tools, therapeutic use of biological products from human origin. The use of PBPC was born in a context where advances in cell biology allow the ex vivo manipulation of cell products in order to change the therapeutic biologic characteristics of cells. Although a lot of other human cells could be experimented for therapeutic use, the PBPC became the main source of ex vivo manipulation because of the easiness of their harvest (13) and were considered as the main « products of cell therapy ».

The Food and Drug Administration (FDA) defines somatic cell therapy as: « the administration to humans of autologous, allogeneic, or xenogeneic living cells for diagnostic, preventive or

therapeutic purposes. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacological treatment of cells, or other alteration of their biological characteristics. ». This definition suggests that somatic cell therapies differ from simple transplantation in that the cells are manipulated in some substantial way. But, the precise boundary between transplantation and procedures involving sufficient manipulation in vitro to warrant designation as somatic cell therapy remains unclear. PBPC transplantation has been considered as the first step of cell therapy, itself considered as a necessary technical transition for the development of gene therapy.

Gene therapy is a medical intervention based on modification of the genetic material of living cells; cells may be modified ex vivo for subsequent administration to humans, or may be altered in vivo by gene therapy given directly to the subject. The scientific community and the biotech industry currently tend to consider future developments of gene therapy as one of the major innovation in the field of medicine for the next century. Therefore PBPC transplantation has focused the scientific, economic and political interests of all the agents -industrial and medical one- which were interested in the development of therapeutic products from human origin. Rapid diffusion of PBPC can also be explained by the fact that it offers a new technical supply as well as the possibility for the agents to improve therapeutic potential, to develop their activity, and/or to be implied in a profitable marketing strategies of new products.

3. The actors involved and their strategies

In theory, there are many technical stages for manufacturing of cell therapy products: harvest, selection, ex vivo manipulation and reinfusion in humans for clinical use. Each corresponds to a distinct stage for the development of the cell therapy market. A first phase involves the simple extraction and reinfusion of cells without « selection » of specific cells. This phase is long underway with bone marrow and peripheral blood stem cell transplantation and offers little commercial opportunity to drug, device, or equipment manufacturers. Future stages of development will seek to improve upon the results of this basic cell therapy by selecting specific types of cells and/or manipulating them to obtain a specific therapeutic effect.

The next phase of technical development involves the « simple » separation of some specific cells extracted from the body from unwanted cells and fluids. This phase of development should have the largest volume of therapeutic applications of cell therapy. However, the

market is currently limited to bone marrow and PBPC transplantations. The market will be derived from two types of bone marrow transplantation and PBPC transplantation, allogeneic (donor derived) and autologous (derived from self). These can be viewed as separate markets with distinct product benefits meeting distinct unmet needs. The clinical benefit associated with cell separation in allogeneic transplantation is expected to be very great.

The third phase of the cell therapy development is the one of the ex vivo manipulation of cells. Ex vivo expansion is a medical Holy Grail of sorts because it would allow avoidance of systemic cell growth factors and provide virtually immediate and complete restoration of the desired cell population. This phase is likely to be very important because it should allow the cells to have some new therapeutic properties that could improve their efficacy. Furthermore, ex vivo manipulation is the first breakthrough in direction of gene therapy.

All these different development phases imply active collaboration between the different actors involved. Actually, the field of cell therapy is a particularly good example of a new type of links between science and technology. In this field, clinical units, public research laboratories and firms are involved in an « innovation network » at each stage of development and distribution of the products. At the beginning, cell therapy and gene therapy were essentially a scientific research topic. Scientific advances in the past decade have made the clinical testing of cell therapy and gene therapy a reality. By the early 1990s with the growth of clinical trials, clinicians became involved in the innovation process and started to apply cell and gene therapies to a wide range of clinical problems. As a consequence, the research agenda appears to have shifted, with an increasing emphasis on application to a number of diseases, in particular cancer, in parallel to the pursuit of basic research investigations.

At about the same time as the first clinical trials using cell products were initiated, dedicated firms started to pay increasing attention to how cell and gene therapies might be used routinely in clinical work and how they could market profitable products. Cell therapy has attracted much attention in investors' minds as a potential blockbuster. With the creation of biotechnology small-size firms interested by this field, a new set of actors entered the innovation process, with both the capacity to carry out research and a clear aim to develop it in such a way that it could be sold as a commodity.

At present, it is difficult to talk about a « market » for cell therapy products – even less for gene therapy products –, or even to be certain about how they will be used in clinical practice,

as no one is able to predict which technologies can be demonstrated to be safe, efficacious and cost-effective in clinical trials. So, the strategies of the involved players incorporate different uncertainties and expectations as to the possible paths innovation may take, as to the different forms of co-operation that may be possible with other partners, as well as to the legal status of cellular therapeutic products and the extent to which they will be regulated.

Because cell therapy allows therapeutic modalities to be applied to a lot of diseases and because it supposes that cells are collected from and reinfused to patients, clinical units are directly implicated in this type of activity. Health care centres wish to keep the control of this new therapy. Thus, they develop an applied research with clinical trials and thanks to research laboratories, which are often present on their site, they conduce too a basic research in the field of cell manipulations.

Each technical step of cell therapy supposes the setting up, the validation and the production of medical devices that could only be done by firms. So, there is collaboration between firms and health care centres in attestation procedures of the new knowledge (both basic and technical).

A lot of pharmaceutical firms have invested in basic and applied research in the field of cell therapy. They are adopting two types of commercial strategy to develop cell therapy. Many companies are simply aiming to act as third party suppliers of cell lines for ex vivo procedures. Other firms are establishing their own « cell service centre » or « cell farms » in order to sell the culturing and modification of patients' cells. This latter strategy tries to extend the existing and limited market for commercial services already associated with bone marrow transplantation. For these firms, the commercial « Holy Grail » is the development of therapies which can be sold as conventional pharmaceutical products. However, the legal status of the product will have to permit that.

4. The problem of cell therapy regulation

The French « bioethic » laws of July 1994 did not manage to give a clear definition of the legal status of the cell therapy products. These laws precise that cell therapy products should have been regulated as drugs but can not specify in which conditions, and left opened the possibility to assimilate them to blood products and even organ transplantation. In practice, it meant that at least three public regulatory agencies, affiliated with different ministers and administrative departments (Agency for Drug Regulation, French Agency for Blood Supply, French Agency

for Transplantation) shared the responsibility for controlling this innovation and could claim for leadership in this process.

In the USA, the cellular products used in somatic cell therapy and the gene therapy products based on viral vectors meet the general statutory definition of biologic products and are subject to regulation by the FDA. But, some products could also be regulated as drugs, e.g., gene therapy products such as chemically synthesised products meet the drug definition but not the biological product definition. In fact, some products may even be considered as a combination of biological products and drugs or devices. Ex vivo cell processing that involves expansion, selection, encapsulation, or pharmacological treatment is viewed by the FDA as a manufacturing step that results in a product for somatic-cell therapy. Similarly, processing that alters the biologic characteristics of the cells - i.e., by inserting genetic material, inducing differention or activation, or causing the secretion of biologically active factors - defines the result as a product for somatic cell therapy. However, unmodified autologous or allogeneic bone marrow cells used for transplantation are not considered regulated products for somatic cell therapy.

Therefore, whatever the current legislation, uncertainty is persistent about the legal status of the cell therapy products which, especially in the case of France, creates a lot of uneasiness among the different agents, from the public and private sectors, who are involved in the R&D process of this biotechnological innovation.

III. Bargaining processes in the case of R&D

1. A general class of models

Our point of departure in this research has been the idea that recent advances in economic bargaining models, taking into account the link between knowledge sharing and development stage, may be helpful to contribute to current debates about regulation of biotechnology innovations.

Of course, because there is an important public good dimension in production of any research knowledge, bargaining models in the field of R&D consider this dimension. But, in the specific field of cell therapy, an additional issue lies in the uncertainty associated with the legal status of cellular therapeutical products: the sharing of the expected surplus from potential invention

depends on the different hypothesis over the possible status of the product. If the product is a drug, firms will have the bargaining power; if it is not the case, health care centres will have the best position in the bargaining process. In our model, we introduced this uncertainty about the legal status of the final product according to the previous empirical observations that were reported above.

Moreover in the case of cell therapy, the participants do not have the same positions in the R&D game: the health care centres control the production of scientific knowledge while the firms favour in priority the technical development of final products. But, both agents are involved in attestation procedures which establish an intermediary knowledge level for one of them and a preliminary stage of the development for the other.

To contribute to the debate about cell therapy, we tried to expand the application of bargaining theory to research joint ventures in the particular case of relationships between pharmaceutical firms and health care centres. We therefore propose a model of a strategic bargaining between agents having different information levels and creating together a public good. This bargaining is over the sharing of the expected surplus from the creation of this good. We only consider 2 agents, a health care centre and a pharmaceutical firm who share the same opinion on the expected value of the developed products. We should precise these assumptions later.

In recent papers (14), an interesting approach has already been applied to the problem of dividing the expected surplus from ultimate R & D among generators and utilizers of basic knowledge. In essence, this approach is to consider bargaining solutions among these agents. The focus is again on the effect of alternative sharing rules and ownership structures on efficiency in knowledge utilisation, as well as incentives for knowledge creation. However, in these previous approaches, the problem of bargaining over transfers of knowledge is considerably simplified, by assuming that an informed agent who generates basic knowledge is unable to develop it further into a marketable invention, whereas an uninformed agent who can do such development work is incapable of having generated basic knowledge. As a result, the problem of bargaining among these agents over the surplus from the ultimate marketable invention is reduced to one of complete information, following upon the disclosure of this knowledge by the basic research unit. An important public good dimension of research knowledge is omitted in this approach.

Other recent papers (15) have examined a bargaining over the surplus from the ultimate marketable invention among agents who do not have the same knowledge state. Both the

possessor of superior basic research knowledge and the other agent are capable of development work on the ultimate invention. The consideration of this assumption allows to examine issues pertaining to the modelling of the bargaining problem as one of incomplete information across participants. This analysis suggests that the informed party will be induced in equilibrium to reveal all its knowledge, and yet retain no surplus. The model, which is presented here, is close to this latter case.

2. *A bargaining model with uncertainty about knowledge and surplus sharing*

We consider a R&D game where two participants are both engaged as in the process of knowledge accumulation (basic research) and of industrial development, the conditions under which future outputs will be shared remaining indeterminate.

Agent 1 is a research laboratory of a health care centre engaged in a research process, whose results could be marketable products. Agent 2 is a pharmaceutical firm whose the main activity is the industrial development, but who invests too in the research process.

We consider $\Theta = \left[\underline{\theta}, \bar{\theta}\right]$ as the ordered set of knowledge levels. Each knowledge level θ could be considered as the probability of getting an invention. We assume that when a knowledge level θ is known, the interval $\left[\underline{\theta}, \theta\right]$ is known.

Each agent is endowed with a knowledge level issued of its personal research efforts which represents a probability of getting an invention.

Let us consider $\theta_1 \in \Theta$ as the knowledge level of agent 1 and $\theta_2 \in \Theta$ as the one of agent 2. Costs, which correspond to these knowledge levels, respectively for agent 1 and agent 2, $K_1(\theta_1)$ and $K_2(\theta_2)$, represent the expenditures engaged in the research efforts.

The individual knowledge endowments are the private information of each agent. We assume that the knowledge state of agent 1 is superior to the one of agent 2, that is $\theta_2 \leq \theta_1$. Thus, only the private information of agent 1 is important. To simplify, we make as if the knowledge state of agent 2 is fully known.

Both agents are assumed to be risk neutral and to have the same opinion concerning the monetary value V of the product, which could be issued of the research process.

The basic knowledge state which is necessary to obtain a developed product, is not the direct result of individual research processes. Development requires attestations, which are realised during clinical trials conducted by both the health care centre and the firm. An attestation procedure is formally a function τ, which is defined in Θ and takes its values in Θ, where $\tau(\theta)$ is the common attested knowledge, which corresponds to the initial knowledge θ.

The knowledge state $\tau(\theta)$ is a public good because it corresponds to a common probability for the participants to result in an industrial development. We admit the function of attestation τ is such as $\forall\theta, \tau(\theta) \leq \theta$. We admit too that the function is monotone: if $\theta' \leq \theta$, the attested knowledge corresponding to θ' can not be superior to that corresponding to θ : $\tau(\theta') \leq \tau(\theta)$.

More than the higher knowledge state, θ_1 which is the private information of agent 1 could not be attested. If no attestation, each agent would take care of the cost of him individual research, respectively $K_1(\theta_1)$ and $K_2(\theta_2)$ for agent 1 and agent 2. If attestation, there is a bargaining between both agents over the attestation and the sharing of the expected value V of the final product.

Let us consider a function $f:\Theta \to [0,1]$. If c in Θ is the level of the attested knowledge, f(c) will be the proportion of the value V paid by agent 2 to agent 1 at the end of the bargaining. We have here a static approach to the knowledge bargaining game. The bargaining is a mechanism (f, τ,p) where p is the probability that this bargaining ends up in a success. Then, the function $p:\Theta \to [0,1]$ gives the probability p(c) that there is an agreement between the participants if c is the level of attested knowledge.

Let us consider now the constraints of our bargaining problem. We define first the ex-post payoffs for both agents, with c as the level of the attested knowledge, f as the sharing function and θ_1, θ_2 as the private information.

$c\big(f(c).V - K_1(\theta_1)\big) + (1-c)\big(-K_1(\theta_1)\big) = V.c.f(c) - K_1(\theta_1)$ for agent 1,

$c\big[\big(1-f(c)\big).V - K_2(\theta_2)\big] + (1-c)\big(-K_2(\theta_2)\big) = c.\big(1-f(c)\big).V - K_2(\theta_2)$ for agent 2.

In what follows we assume, w.l.o.g, that V=1.

Payoff of agent 1 before the bargaining is given by:

$$p(c)\big[c.f(c) - K_1(\theta_1)\big] + \big(1-p(c)\big)\big(-K_1(\theta_1)\big) = p(c).c.f(c) - K_1(\theta_1)$$

Payoff of agent 2 before the bargaining is given by:

$$p(c)\left[c.(1-f(c))-K_2(\theta_2)\right]+\left(1-p(c)\right)\left(-K_2(\theta_2)\right)=p(c).c.(1-f(c))-K_2(\theta_2)$$

The knowledge level of agent 1 is a private information, which has to be disclosed during the bargaining. So, the bargaining will impose on agent 1 an incentive constraint. This constraint is such as agent 1 could lose everything if he does not submit his private information to attestation. So that:

$$\forall\theta_1, \forall\theta' \le \theta_1, p\left(\tau(\theta')\right).\tau(\theta').f\left(\tau(\theta')\right)-K_1(\theta_1) \le p\left(\tau(\theta_1)\right).\tau(\theta_1).f\left(\tau(\theta_1)\right)-K_1(\theta_1) \quad (1)$$

The bargaining will impose too on agent 1 an individual rationality constraint such as he has to cover the cost of him individual research in all hypothesis:

$$\forall\theta_1, \forall\theta' \le \theta_1, \tau(\theta').f\left(\tau(\theta')\right) \ge K_1(\theta_1) \quad (2)$$

Agent 2, whose the knowledge state θ_2 is known, has got some beliefs about the agent 1' knowledge state. For this agent, there is only one individual rationality constraint where the conditional probability considers his beliefs about the agent 1' knowledge state:

$$E\left[\tau(\theta').\left(1-f\left(\tau(\theta')\right)\right) \Big/ \theta_2\right] \ge K_2(\theta_2) \quad (3)$$

To analyse the bargaining strategic aspects, we consider mechanism with sharing functions f, attestation procedures τ and success probabilities p. Its elements respect the individual rationality constraints, the incentive constraint as well as the property of efficiency.

The expected surplus from potential invention which corresponds to a mechanism (f, τ, p) with an attested level of knowledge c, is given by:

$$p(c).c.f(c)-K_1(\theta_1)+p(c).c.(1-f(c)-K_2(\theta_2)=p(c).c-K_1(\theta_1)-K_2(\theta_2)$$

According to the efficiency property, the surplus has to be the bigger as possible, so that:

$$p\left(\tau(\theta')\right)=1, \forall\theta' \le \theta_1 \text{ et } \tau(\theta')-K_1(\theta_1)-K_2(\theta_2)=\tau(\theta_1)-K_1(\theta_1)-K_2(\theta_2)$$

We will admit that the attestation procedure is always compatible with the condition to generate a surplus.

In our model, we verify that whatever the proportion of surplus agent 1 or agent 2 could obtain, an efficient bargaining (p(c)=1) with an attestation procedure which satisfies the

condition to generate a surplus, gives an efficient mechanism which is incentive compatible and individually rational.

Let suppose indeed we have p(c)=1. We seek the functions f and τ which satisfy the 4 following conditions, $\forall \theta_1, \forall \theta' \leq \theta_1$:

(1) $\tau(\theta')f(\tau(\theta')) \leq \tau(\theta_1)f(\tau(\theta_1))$

(2) $\tau(\theta')f(\tau(\theta')) \geq K_1(\theta_1)$

(3) $E\left[\tau(\theta').(1-f(\tau(\theta'))) \middle/ \theta_2\right] \geq K_2(\theta_2)$

(4) $\tau(\theta_1) - K_1(\theta_1) - K_2(\theta_2) \geq 0$

We consider the set of the sharing functions f_α, $\alpha \in [0,1]$, such as $f_\alpha = 0$ (resp. $f_\alpha = 1$) if α=0 (resp. α=1), which are build in giving to agent 1 the following surplus part:

$$\alpha\left[\tau(\theta').f_\alpha(\tau(\theta')) - K_1(\theta_1) + E\left[\tau(\theta').(1-f_\alpha(\tau(\theta'))) \middle/ \theta_2\right] - K_2(\theta_2)\right] \quad (5)$$

So, when α=0, agent 1 receives nothing and has to meet his costs and when α=1, agent 1 receives the maximal possible part of surplus.

Such sharing functions are compatible with the efficiency as soon as c is chosen in order to satisfy (4). It is easy to see these functions verify (2) and (3). The incentive constraint (1) is too satisfied by such sharing functions because equation (5) imposes on agent 1 to lose everything if he does not submit his private information θ_1 to attestation. Incentives are only about agent 1 whose the state of knowledge is dominant. The part of surplus, which is attributed to other agent being an exogenous data, it is always in interest of agent 1 to increase his own part in increasing the surplus. These circumstances do not contradict a disclosure of his private information. In this context, it seems always possible to set up a bargaining concerning an attestation as well as an efficient sharing compatible with the different constraints.

However, our model is a simplified one, which does not consider a dynamic approach of both scientific inventions and development and interactions between multiple agents.

IV. Conclusion

Cell therapy offers an emblematic case-study for analysing a situation where a technological research is on the borders of both production of attested knowledge and economic incentives with the additional difficulty that it is developed in a sector where private markets, public insurance and public sector overlap. We have considered an economic model where the main strategic aspect is the closed link between the sharing of basic knowledge results and the industrial development possibilities. The main result of our model contradicts the feeling of many actors that current uncertainties about the regulation of new products will negatively affect the R&D process. The model shows, on the contrary, that whatever the part of surplus which is given to one or the other agent, it seems always possible to set up an optimal bargaining concerning an attestation and an efficient sharing of surplus compatible with the different constraints. Therefore, any unilateral solution about the legal status of the cell products could block both the R&D process and the necessary co-operation between public actors and firms.

Although far from being satisfactory from a theoretical point of view, the confrontation of our bargaining model with the empirical situation in the field of cell therapy has direct implications in terms of policy recommendations. It suggests that maintaining some flexibility, and even some space for ambiguity, in the regulatory status for new biotechnology products, such as cell or gene therapies may indeed be useful for improving efficiency of the innovation process. It also suggests that legal assimilation of an entire new class of therapeutic products from human origin to already existing drugs or devices may be totally inappropriate although spontaneous attempts to regulate by extension of existing legislation are often frequent.

In 1996, a bill was introduced in the French Parliament, in name of safety considerations, which would have assimilated cellular products to ordinary drugs, therefore implying asymmetries in favour of drug companies in the bargaining power. Fortunately, the bill was not accepted and in agreement with our recommendation, French legislators created an intermediary specific status for cell therapies. This is in line with FDA decisions, which consider that cell therapy products meet the general statutory definition of biologic products. However, the fact that the practical responsibility for regulating these products was given to the French agency in charge of control for drugs suggest that the debate has not ended and that

sociological factors and political rationales still threaten the conclusions of economic analysis, especially in the field of medicine and health care.

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