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Producing 'Human Elements Based Medical Technologies' in Biotech Companies: Some Ethical and Organisational Ingredients for Innovative Cooking

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Almost all of the empirical studies on bioethics deal with the general people's attitude to social issues like medical diagnosis, abortion or procreative technologies, for example; alternatively, they focus on institutional production of ethics coming from advisory boards, regulatory committees, etc. So, despite the persistent interest in the recent emergence of this plural field of discourses and practices related to bioethics concerns, the main stream of studies consists in understanding how actors respond to some social alarms and describing the kind of devices, organisations and public policies developed by actors to define and manage what they identify as bioethics issues (for an interesting inventory of literature: Kelly, 2003, pp. 339–364; Pickersgill, 2012, pp. 579–603). Some other studies mention the performative effect of the circulation of ethical statements, so they point out to their relative autonomy to instances producing them. However, the bioethics production plays locally, among professionals involved in companies' activities linked to the daily practices. It does not limit to the actions of more global institutions (committees, national procedures, etc.). We would suggest considering that the bioethics phenomenon is more than a collective/state/institutional answer socially constructed and applied to a well-known pre-existing situation. For this reason, we investigate the field of emerging technologies within private companies. We argue that bioethics constitutes an inherent component of the qualification process of controversial technologies and that its expression directly reflects the level of imprecision and uncertainty associated with the technical devices under controversy. For example, the 'nano' label is used to qualify practices where the definition, the outline of disciplines involved, the physical infrastructure and the concrete applications appear to be far from being settled in the eyes of those who produce them, including the scientists themselves. Such a label covers without distinction common routine practices as well as innovative laboratory research projects. Since nonotechnologies have become a tangible reality, they have been spontaneously

integrated into a formalised dialogue and placed under the responsibility of public authorities, as evidenced for instance by the 'NanoDialogue' operation financed by the European Commission. This initiative formulates hopes and concerns—taking a pedagogical stance and checking (questioning?) conformity to ethical rules. But this ethical production is not closely related to a well-defined 'material culture'[1] or well-stabilised practices. It rather applies to the large—and somehow blurred—set of practices labelled as the 'nano' field.

This article challenges the idea that bioethical statements are elements of a discourse, which simply masks economic and industrial interests. Adopting a pragmatist approach of the 'ethical' realm of language and practices, this article attempts to show how issues in bioethics are more than that. Starting from issues associated with emerging technologies, we will demonstrate how the moral order is inextricably linked with their future implementation into a market (Hilgartner, 2004, p. 141) and how the importance given to this discourse directly reflects the state of advancement of the technical processes related to the controversial object. In the case of medical use of human cells, for example, bioethical debates determine how these cells can be considered as a part of a medical technology. We argue first, that bioethical statements are not an external judgement applied on a predefined category or technology and second, that they act as a political standard (Tournay, 2008, p. 237) that enables the stabilisation of medical knowledge and its organisational practices. From this perspective, bioethical concerns appear as a means of describing the organisational conditions under which the innovative medical practices became possible (Mahalatchimy, Rial-Sebbag and Cambon-Thomsen, 2011, p. 163). More specifically, ethical issues describe the interface between an emerging medical technique and the public or private instrument that would control it, so they act as a boundary object (Star and Griesemer, 1989, p. 387), in the sense that we consider some of these statements as language entities simultaneously shared by several different communities but viewed differently by each of them. Bioethical concerns help in assigning a social label to technologies that exist only in the form of projects developed from laboratories such as gene therapy, human Embryonic Stem Cell research or therapeutics based on nanobiotechnology products as we will see below. Through this argument, we enlarge Timmerman's and Berg's categorization of standards[2] (2003, p. 24) by associating statements about expectations, especially ethical ones. We show that bioethics intervene as a kind of descriptive, explicative and predictive narratives that are ingredients of the context (Law and Moser, 2012, pp. 307–331).

The aim of this study was to examine the way in which bioethical concerns take shape and develop in European private biotech companies—a field poorly explored by social scientists. A comparative analysis was undertaken in various European countries within companies working on a wide range of emerging technologies which use human materials (human tissue diagnostics and biomarkers, nanobiotechnologies, storage of human biological material and preparation of cell therapy products, research based on embryonic stem cells) or include human subjects

(clinical trials). These controversial products regularly challenge the organisations in charge of their regulation. The study was carried out in five different countries using interviews: France, Italy, Sweden, Hungary and Belgium. Our interviews give a representative picture of the diverse settings of biotechnology production in the countries under study; they were then used as a basis for a large scale data collection. The aim of the qualitative analysis is an in-depth exploration of the nature and importance of the particular ways in which ethical reasoning evolves in the production process of emerging technologies. The findings will be discussed along case studies of practices based on ethical statements and in relation to their local national context. The primary corpus of texts arising from the interviews has been used with the purpose of drawing up a more general questionnaire to be sent to a wider group (around 60) of companies.[3] Its preparation was based on the discussions about ethics recounted by those of the interviewees who had had a significant part to play in setting up their practices. The responses to the interviews were subjected to a careful analysis allowing then the drawing up of the questionnaire. On the one hand, the analysis involved the manner in which the interviewees expressed the bioethical questions, which might arise in their companies, or their field of activity, with regard to a number of factors as well as the means of resolving these questions and of implementing solutions into concrete practices (1). On the other hand and from the responses given, we then identified the references on which the various means of resolving the bioethical questions were based (2). These complementary approaches allowed us to check whether the elements obtained during the interviews for each biotech sector were representative and determined what stands out as the decisive ethical standards for the sectors of activity studied. This allowed consequently to distinguish the more anecdotal elements from those more specific to a given company. One will see here the interest of studying local discussions about ethics, which emanated directly from the production sites to draw up a research methodology around these questions that remain difficult to grasp. By paying particular attention to each local scene, our bottom-up approach directly questions the link between good ethical practices and the actual degree of progress in the technology under consideration and more generally, the link between technical possibilities and moral decisions or intellectual properties (Barry, 2001, pp. 104–124; Noble, 1984, pp. 42–46). But there is more to be discovered from such an approach. The body of interviews conducted with directors of biotech companies is above all rich for the ‘historical dimension’ of their bioethical practices. It gives us a good insight into the manner in which ethical concerns and the company production have taken form over time (3). The longitudinal dimension of the study is difficult to grasp by exclusively basing the analysis on a questionnaire, even if a broad sample of companies is included. Such a dimension, however, is necessary for establishing a co-production model of moral statements and material practices, as Margaret Lock shows for example, between the transformation in transplant practices and the benchmarks of death (Lock, 2002, p. 32).

Ethical Stakes: External Judgements or Industrial Activities-based-statements?

Interviews were designed and conducted so as not to influence the responses. Therefore the questions contain as little a priori as possible in the manner of designating what the term 'bioethics' covers, as well as no specific indications concerning legal tools or historical reminders which could be seized upon by the interviewees. This does not exclude taking into account the professional career and specific expertise of the people interviewed to understand the way in which they define their bioethical concerns. Thus, the corpus obtained from interviewees with a medical background was more centred on the expectations of the patient (many have based their project on therapies applicable to rare and lethal diseases) than the one obtained from biologists, whose aim was to provide guarantees related inclusion of ethics involving a technical process. The two following extracts illustrate these different orientations; first (A), with a business manager who has a medical background:

> The whole problem with the embryonic solution, it is going exactly as it did for gene therapy, the problem of the stem cell, which becomes an effective treatment […] I mention this because previously I worked on in vitro fertilization […] and therefore I am returning to my first love, so to speak.[4]

Second (B), an interview with a business manager who has a background as a biologist: 'Now, in our particular case, I think that what you call bioethics is part of the classic process of good development'.[5]

Our framework includes questions concerning emerging contexts, organisational features and fields of expertise of biotech companies to precisely reconstitute history of organisational characteristics of companies and of the technical processes within them. We asked actors to describe the conditions and pragmatic features of bioethical issues within companies such as emerging guidelines as 'good' standards of practice.

Initial interviews carried out concerning the occurrence of bioethical issues within companies show that for industrial stakeholders, ethics is neither a simple judgement applied to objects, nor a collection of reasoning processes that are isolated from the rest of industrial activities. Various elements which came out of the interviews show this strong overlapping between the production of reflections about ethics, the social context and the scientific beliefs of the industrial actors. First, there are no specific concepts or terminologies used by the actors to describe the intrusion of bioethical concerns in the setting up of their activities. Some feel uncertainty as to what the term covers: 'I don't think (we have any new bioethics problems now). Do you?'[6]

In fact, as various actors (C, D) pointed out, it is a term, which is not spontaneously used:

> I don't really see the difference between bioethics and what I believe in on the medical and scientific level. For me, the term bioethics is a bit like the term

nanotechnology, it covers everything and nothing. And for me, without looking at the definition or anything, that calls for common sense, respecting the people who will be interacting with what we are doing, in the widest sense of the term, not just purely the product and the use of the product.'[7]

Then, the type of ethical rules and regulations described by the actors is strongly linked to the emergence of biotechnologies in a specific national context (in particular to the type of technical process). This is reflected upon a very great diversity of what the actors mean by bioethical concerns in companies:

A lot of new issues will be affected if you are aiming for cell therapy and regenerative medicine […]. When we are facing the industry to work with these cells as an in vitro tool for industrial applications, the issues we are facing are much smaller.[8]

Lastly, despite the diversity of industrial context, the term 'ethics' is more frequently associated with certain words or group of words in the corpus of texts, such as: 'patients,' 'clinical trials,' 'embryonic,' 'consent,' 'communication,' and 'information'. For most interviewees, the notions of communication and information are linked with the constitution of a realm of ethics at various levels. If communication is envisaged as generating a flow of information towards the public in the widest sense (including care centres, health professionals and patient associations), the notion of information refers more specifically to aspects concerning the protection of persons and consequently tends to refer more to the regulatory requirements that are involved. These two notions are thus present throughout the process of manufacturing a product for innovative treatment and bring into play a diversity of actors, ranging from the research community to the patient and to the public sphere. They are found in the properties of products under development:

Interview E: 'We communicate, for example, very little concerning the results of our research. We communicate almost exclusively on the products which move into clinical use […] There, that's something we are asking ourselves these days—should we not communicate earlier concerning our programmes? […] There is a dimension which involves the scientific community and the community at large.'[9]

These notions are also found in the context of consent:

Interview F: 'We will always be working with the approval of the ethics committees who look at all the contracts which are drawn up […] And if something is not right, it will punish the person. The first time we inform [them?] because we don't want to have any problems concerning reputation in this field. Because it's really against our spirit and our values.'[10]

And for immediate communication with the patient, as a geneticist (A) told: 'You have to speak to the patients. So I did, and now all those who were in this pro active context, at the beginning of the 1990's, are now the major players on the side of the patients at the European level.'[11]

Ethical considerations are a means of communication with the public too. In this case, the need to communicate is found in the actual organisation of the company. This necessity may be formalised by the presence of a person in charge of communication, or by the existence of a commercial network (communication marketing) attached to the company. The significance of some ethical concepts related to the way of communicating is plural. The sense given to informed consent varied upon according to the biological product concerned and its use. The significance functions of patient consent described by interviewees differ when it is consent for inclusion in a clinical trial protocol, for the donation of elements for diagnostic purposes, for an anonymous donation or for an auto-transplant. In the first case, consent arises as a standard required for the proper production of the product:

> Yes, yes everything we do is obviously under very strict (surveillance), because we are regulated as a medical product and we want to play the game according to medical products so everything we did in the clinical trial was (...) it's obviously they are the highest standards.[12]

In the case of donation for diagnostic purposes, informed consent enables a delegation of responsibility to the people carrying out the research:

> We decided from the outset that, with informed consent, it was the geneticist who would transmit the results to them [the patients], because they of course have the right when the results are in, of knowing what those results are. But us, we don't want to go there, that is not our role. However we do need to ensure that things happen like that, that the tests are done, that there is a return, that there is genetic counselling at the end. But it is true that it is very sensitive. For us, without informed consent it's very difficult![13]

The significance described differs also if the company is involved with a biological product deriving from a donation and destined to be re-injected into the patient or not and if, in the latter case, the re-injection of the product falls in the context of a life-threatening disease for that patient. In this case, consent offers greater flexibility in the preparation of the product: 'If patients need a solution, sometimes you need to continue on with them in order to develop something, without really knowing where you're going because it's research. But the important thing is that it is the patient him/herself who gives their consent'.[14]

In any case, consent is mentioned as being essential to protect the wishes of the people who are sources:

> We have developed ethical guidelines that apply to sort of the common sense in the area, but also to the laws and legislation in all these countries. That is, for example, that we have to use informed consent, that has to be signed by both parents who donated the fertilised egg. In this informed consent it should state exactly what will be done with the cells, that the cells are going to ---, that it is a commercial entity, we are going to do this, and this, and that, with cells, we maybe have to send them abroad and most importantly we are going to earn money using these cells.[15]

By providing basic standards and by mobilising various persons about consent forms, the uncertain process of the production of new knowledge becomes more stable (O'Connell, 1993, pp. 159–162). Actors are then engaged by the same material representation of the scientific entities and processes. With this 'disciplinary objectivity', the production of 'true' superimposes on the 'procedurally correct' in the construction of the technical devices (Porter, 1994, pp. 197–238).

Ethics provides a good indicator for assessing the stability of a given socio-material arrangement. Unlike the production of recommendations for institutions which places all practices whatever their effective stage of implementation or their scale of applicability on the same level of reflection, local discussions concerning good ethical practices to be adopted refer immediately to the actual degree of progress and development of the technical process. In fact, the ethical approach to understand and define the medical environment can be interpreted as if it were a principle of 'social connection' (Latour, 2005, pp. 25, 88). Gathering questions about ethics and the form of resolution adopted by biotech companies aims at getting away from top-down reflection, essentially based on a conceptual definition of each of the biotech processes considered (this is particularly striking in the nanotechnology sector) in order to tie particular discussions more closely to the concrete reality of the technical process. Ethical statements cover a plural and heterogeneous reality. It is loosely related to the training and beliefs of entrepreneurs but rather highly related to the characteristics of their firm activities. It also provides an alternative perspective to top-down reflections, as they are essentially based on a conceptual definition of the biotech processes and widely detached from the concrete practices at stake. This is particularly striking in the nanotechnology sector where concrete practices are far from settled for those who comment them from the point of view of ethical considerations.

Producing Ethics Within the Companies: A Variability of Text References and Arenas 'Without Borders'

The references mentioned as being 'sources for ethics' are very variable (Memmi, 1996, pp. 1–254), ranging from binding legal instruments (laws, directives) to professional recommendations (FDA, Guidelines, Charters, the bioethics group of Europabio, etc.). It should be noted that only two companies spontaneously mentioned ethical recommendations as being a source on which they could rely.

Moreover, the ethics committees mentioned are those whose guidance is sought for a research protocol, so it is from the angle of research and clinical trials that ethics bodies are integrated into the debate: 'As soon as you start working with patients and even before, in preclinical, you have questions, so you have to go to the ethics committee.'[16]

One does not deny the influence of highly institutionalised generic procedures such as those from committees and legal production in general. But the function of these instruments is also envisaged in different ways. In the majority of cases, the people interviewed made compliance with the law (European or national) an absolute requirement. A number of scenarios were mentioned. A first case scenario: A law exists and under no circumstances should it be departed from, even if the conditions laid down by law are not always clear: 'My form of ethics is that the framework of the law must be upheld' and 'we don't want to go against the law so we want to do everything very legally. Sometimes it's not clear what is legal.'[17]

A second scenario addresses the absence of a law. This occurs when a particular bio-tech sector is seen to be in a kind of regulatory vacuum and the regulatory institution is questioned and often seen as the right partner to adopt behaviours which would not be challenged further. A company may also internally develop means to resolve conflicts regarding ethics, which can be particularly keen in sectors where various contradictory rules and regulations are referred to: 'We have developed ethical guidelines that apply to, sort of, the common sense in the area but also to the laws and legislation in all these countries.'[18]

It shows the importance of guidelines where there is no law. Ethical guidelines have been developed in an unregulated area but without contradicting existing laws and in accordance with enforceable and recognised general legal and ethical principles. Conversely, European Union rules are certainly appreciated as a resource through the adoption of Directives (notably that concerning clinical trials), but continue to raise questions as to the real harmonisation they are supposed to produce (for example, within the framework of the 'Tissue and cells directive' 2004/23/EC). They are seen as a resource for ethical guidance in that they are supposed to harmonise Europe's regulatory landscape through the adoption of shared directives by the member states. However, they were questioned by the interviewees, as to whether or not they will be able to produce real harmonization effects (e.g., within the framework of the 'Tissue and cells directive' 2004/23/EC). The reasons mentioned are either that all the provisions of the directives have not been transposed into the Member State's domestic law, or that transposition is variable in each State (incomplete, incorrect and/or different in the level of transposition).

The ethical requirements, once identified within a company, are then pooled within the company itself in various forms, which are more or less organised. Globally, these arenas for discussion are not very formalised, without edges and seams, with perhaps the exception of the ethical questions concerning animal experimentation. Often there will be a specific committee within the company to deal with this particular question. Despite this, however, there is not a standardised physical representation of an area for ethics in companies. More generally, these discussions tend to take

place in team meetings with a link to hospital structures when the patient is at the end of the production line. The physical representation of ethics can also be the presence of persons with the legal expertise and knowledge on ethics:

> Interview G: 'These two ladies (that are our legal department), they are educated in of course legal, formal things but they have also been educated in legal aspects and ethics of human embryo stem cells. They have attended courses and congresses on this topic for many years.'[19]

Some Ethical Standards for Technical Devices and Organizational Coherence

The various actors expressed in different ways the bioethical questions they might have to deal with and specified the context in which they came to the fore (medical discussion, respecting quality standards, etc.). Despite the heterogeneity of the epistemic positions and of the material cultures involved, several entities influence how bioethical discourses are shaped.

It was shown that the standardisation of the technical process is highly correlated with the production of scientific objectivity (Latour, 1992, p. 296; Tournay, 2007, pp. 265–267). Our current study shows that the '*level of automation of the production line for biological products*' defines a component that comes into play in the structuring of bioethical concerns. Emerging technologies are more or less defined in terms of stabilised processes and methods. Production of diagnostic kits for genetic disorders and infectious diseases illustrate the first tendency. Actors aim at improving existing automated processes in order to accelerate technical procedures, to improve the sensitivity of a test, then to apply it to the tests for candidate target molecules. In the case of less standardised processes, such as technologies based on a nano-metric scope, the industrial challenge lies in turning nanobiotechnologies into a tangible innovation. Unlike the processes of nanobiotechnology, the production of diagnostic kits targeting the identification of genetic disorders and infectious diseases is fully automated. It requires instruments for measuring and detecting gene amplification based on PCR procedures, biochemical detection of pathogens, molecular screening, robotised test systems on a large scale, etc. All these features are well-known today and found throughout research laboratories and in pharmaceutical companies. Some actors alluded to the importance of 'procedural design' in the production of ethics. 'Obviously the whole aspect around clinical trial design, it's always an ethical question.'[20]

This refers to the arrangement of actors who are involved in the technical procedure under consideration (Louvel, 2012, pp. 21–24). In the example above, it is notably the organisation of trials based on autologous elements, which is compared to those, based on allogeneic elements. Obtaining consent is considered differently in this process depending on the source of the biological material. The arrangement, the design is an ethical issue in itself for the actors involved.

The 'wide diversity of biological samples' stored is another important factor that interferes with the production of bioethical norms. Actually, there is a lot of tension

between the production of common ethical recommendations and the diversity of procedures for managing the specimens (Rial-Sebbag and Cambon-Thomsen, 2012, pp. 113–130). These tensions focus mainly on the negotiations and establishment of standards for consent according to the type of biological element and the occurrence of new therapeutically oriented projects or the renewal of a using authorisation. In addition, the ethical questions which emerge, in particular when the companies store or use cell lines (whether embryonic or not), are in majority related to the legal access and use of such cells, to questions concerning the embryo, to the marketing and to the original ownership of these cells, for example, *'it's the patient's own material'*. Whereas the questions raised by the storage of DNA refer more to problems relating to the protection of persons who are sources of material and their data confidentiality:

> The bank, at the start, because right from the outset we said, we were indeed concerned over the patient to whom this material belonged, what we could do with it, how we could use it, with the necessary authorization and so forth…' and 'It needs to be the patient who is at the centre of this ethics and we need to see with the patients how it will be possible to manage the whole thing, this is capital…[21]

As we just underlined, the nature of the products stored strongly influences the bioethical concerns raised within the companies. This production of ethics is equally related to the 'value' (Cambon-Thomsen, 2007, pp. 373–375) that interviewed persons attributed to 'collections of biological material'. Our corpus shows a diversity of situations in relation to the banking of biological material, especially, to how the 'bank' is organised within the company. Some interviewees link the story of their organisation to the early establishment of a biobank as a resource for the development of subsequent activities. In the following example, the high degree of organisation is linked to the fact that the biobank was initially set up for a serious, rare disorder: 'We were the first laboratory, the first existing DNA bank in France, and we received a huge amount of samples.'[22]

The historical pattern of companies appears key when the establishment of a centre for storing biological material follows the activity of the firm. When developing a technique, some manufacturers harvested specimens that were kept. They then find themselves at the head of a biobank, which has to be legally declared: 'Yes, we have a biobank, a bank which is not declared as a biobank.'[23]

The regulatory aspects and bringing the laboratory in line with the law are often mentioned as being the driving force behind the declaration of a biobank; it is worth doing if its value to research is recognised:

> That's worth a mint, that is! It is a bank, but it truly is a bank! DNA is worth… it's worth a lot, what we've got here! But it's worth a great deal for research, in value', it has to comply with legal instruments such as guidelines ('Tissue banking in Clinical Trials', USA).[24]

We find that the production of ethical standards differed according to the links formed directly 'between patients and the company'**.** Biotech companies which have to deal with a wide population of patients (for diagnostic purposes), with a smaller number of patients (clinical trials), or where their presence is sometimes not required at all (the by-products of embryonic stem cells as a medium for testing drugs) do not formalise bioethics concerns in the same way. In the latter case, ethical concerns are marginal; they are better described as quality control for the by-products of biological material, and as a requirement for international harmonisation regarding these products.

By extension, 'quality control for an innovative treatment' product acquires a strong ethical connotation when it is difficult to obtain, or if its properties are donor-dependent. So, when it has been made from lines of embryonic stem cells or mature cell products difficult to obtain, the ethical issue of the treatment is strongly attached to the way in which the actors measure the quality of a product and therefore deduce the chances of treatment success of the graft in the volunteer patient. According to one testimony concerning cell products to be injected into patients suffering from cartilage damage, the question of ethics was focused on the type of comparator to adopt. Should the effects of the graft be compared with classical standards of care or to treatments that have, neither positive nor negative effect? The answer to this question differs according to the position of the actor in the translational line from bench to bedside. For those who intervene at the end of the treatment line (surgeons in particular) the cell product being donor-dependent, its rarity leads some of these actors to consider that its injection into the patient must only be subordinate to the proof of absence of infectiousness of the product. Whilst for others, its requirement for injection remains indistinguishable from the properties of a good medicinal product regarding the criteria of quality, safety and efficacy. Although intervening at the end of the clinical trial line, this type of concern directly impacts companies that have to perfect as best as possible these cell therapy products to limit discussions regarding the use of the injection (Actor H):

> This is an ethical question which we have not completely resolved, because some surgeons then say, yeah, but these cells are good, they are not infected, they are..., so we think we would still want to give them back to our patients. And I think the answer to the ethical question is that it is then up to the surgeon and the patient to decide whether it is still worthwhile to inject these cells. Because we know and...We will build up the experience that the chances of success are lower, but there's still chance of success. And so then you have to measure what the risk/benefit is. Is it still positive, or not.[25]

More widely, establishing good quality control (drugs tested on embryonic stem cell by-products, or phase III clinical trials on mature cell-based biological products) is an imperative, both technical and ethical. It is evident that the production of ethics is closely linked to quality standards and to manufacturing conditions

(or of culture, for human cells): '[…] This score which gives us a fingerprint of the phenotypic stability […] I think for us, it's mainly the ethical questions about who is the owner of the material, and can we refuse a patient if the quality is not optimal'.[26]

So, the production of ethics is strongly related to the quality control and therapeutic qualities of the product. Likewise, the way in which the 'product must be administered to the patient' influences what the actors describe as being the pin-pointing of an ethical problem. One of the actors interviewed described his ethical concerns related to the absorbency of his biological product as: 'Well, as far as our bio-adhesive tablet is concerned, the bioethical questions that I ask myself are questions, which are somewhat medical: is it going to stick in the oesophagus?'[27]

'The seriousness of the disease for which the innovative treatment may be the answer influences the production of ethical concerns.' The sample of companies interviewed included those manufacturing products for treating injuries, incapacitating diseases and lethal diseases. When the therapeutic product is intended for patients whose life expectancy is short, the benefit/risk assessment for use of the product is modified:

> I work with severe diseases, my patients have six months to live, I am not spreading nanoparticles in the environment, I am putting them into a liver, of a patient who has a life expectance of six months' and 'And there is no other treatment for these patients. To <u>not</u> do it is already a problem.[28]

Lastly, the development of automatic screening processes was carried out in one of the emerging countries in Europe—Hungary—so as to follow the local integration of ethical references already present in the European Union as well as the development of ethical practices specific to these industrial companies. For them, acquiring legitimacy requires to *anticipé* the risks and breaches observed in other countries:

> What happens in England where this extreme situation took place was, there was a big scandal because a pathologist was collecting organs from deceased babies […] And there was a big scandal and this is the backclash now that these extremes are happening and pathologists cannot do a simple extra test […] So we have to prevent this, so we say that such a thing cannot happen to Hungary in a biotech company member of our association then we can say not worry about that because we do oversee this ourselves.[29]

Means of Resolving Ethical Questions by Resorting to Agencies: The Making of Accountability

Although a large majority of the biotech persons felt concerned by the issue of taking into account bioethical questions in their company's activities, the way in

which they attempt to answer these concerns varies significantly from one industrial setting to another. The notion of 'ethical responsibility' is very present. For our interviewees, this notion refers to an external opinion in order to find ready-made solutions, or in order to confirm an opinion formed inwardly.

The means of resolving the problem that were adopted by actors faced with ethical concerns, imply the appropriation of a reference framework which is external to their practices (Granjou, 2007, pp. 135–138). The presence (France) or absence (Sweden) of 'national regulatory agencies' having regulative jurisdiction applicable to a given type of practices: research using human embryonic stem cells, certainly played a role. One of the important ethical issues for all the European companies studied which were working on stem cells concerns the institution of quality standards for the product, for its preparation and its storage. The means of producing ethical practices in Sweden contrast strongly with the French regulatory framework since there are no national agencies applying regulations on human embryonic biological material. The development of research related to this type of material was framed internally very early by the actors themselves by drawing on the existing good practices in North America concerning the management of biological products and consent. Several actors insisted on the necessary collaboration with national regulatory bodies. This collaboration was envisaged at several levels. If there was a deficiency in the existing framework, the collaboration would concern the adoption or the adaptation of the regulations to the sector of activity. Above all, regulatory input occurs principally at two stages of product development. First, it intervenes in the classification or qualification of the product. The interface between the regulatory agency and the company is crucial since the type of guidelines applicable to the product will depend on this classification. This is, for instance, the case of innovative treatments relying on nanotechnologies:

> These internally regulated products are a bit borderline since they act like medical devices – […] Clearly, our products do not interact; their mode of action is not based on interaction with living material. So, we are far from drugs and fully in the realm of the medical device.[30]

Second, the interface between the regulatory agency and the company is a fundamental root for determining the market price:

> **Interviewer:** Take AFFSAPS, for example. What do you talk about with them? Is it, as we were saying earlier on, is it about the classification of your products?
> **Interviewee:** and, licensing […]
> **Interviewer:** The procedure part. And HAS, that's …
> **Interviewee:** The price![31]

Some external bodies, such as 'patient associations' play a role in the production of ethical standards. One of the biotech bodies has the legal status of a non-profit

association. It appeared in France in 1994, the very same year when first regulations concerning bioethics were applied. It is within this structure that good ethical practices concerning access and uses of human body elements were extended to various types of biological specimens (DNA, tissue, body cells, frozen lymphocytes, embryonic stem cells, etc.) and to associated activities (sequencing, genotyping, cell therapy, research on embryonic stem cells). At the same time, a first piece of traceability software for these elements was also established. From the outset it insisted on the responsibility of a professional group faced with patients and focused particular attention on drawing up standards for consent:

> We had consent from the outset. When I arrived, I saw, it was out of concern to see the specimens we were going to give. And there were consent forms, it was special […], it was 4, 5 lines: 'I agree, or not, to donate for research into such and such a disease.' So, right from the outset things were organized with consent. You see, we are a patient association and they are very, very…and that is the privilege…they are very sensitive concerning everything to do with the patient.[32]

Consent forms can be considered as a boundary object because they are used by different communities of donors that have various motivations to donate and each of them does not have necessarily a clear perception of the use of their body elements (Barr, 2006, pp. 251–262). The actors often mention the compliance of their practices with 'legal standards'. This is an active way of reaching a consensus of opinion, and of resolving their bioethical questions. Thus, by complying with a law, for example in the field of clinical trials, means that issues concerning information and consent of study participants can be solved. Law and reflections regarding ethics are thus often mixed up in what the actors say and, even more, their function for the company is judged to be equivalent. But the rule of law has the advantage of coercion force which reflections concerning ethics do not (and do not claim to have). For instance:

> We need to think in a generic manner in the sense that we know perfectly well that laws exist. You can't undertake a clinical trial without talking to an ethics committee. You can't undertake a clinical trial without asking the agencies. So, in a certain sense, we are ethicists without knowing it![33]

For biotech actors, regulation by law is both envisaged as a constraint and a liberating element. This regulation seems to be desired in order to establish stable guidelines:

> In many countries, as in Sweden, Finland, Denmark, France, Belgium, the Netherlands, the UK, they have similar legislation to Sweden, they allow it. Always though, that's important to point out, [...] with very strict ethical guideline. So, that is what we have developed; we have developed ethical guidelines that

apply to sort of the common sense in the area but also to the laws and legislation in all these countries.[34]

In this way, Herbert Gottweis has shown that the implementation of a legal framework related to genetic engineering, in the mid-seventies, allowed scientific actors to define a set of practices based on molecular biology as an integrated political object (Gottweis, 1998, pp. 39–76). Another major aspect is the fact that the absence of legislation makes the position of the companies uncertain, with the result that they will be in favour of a form of lobbying (by manufacturer associations, for example) in order to demand the laws required by their activity. This can be interpreted as allowing questions concerning ethics to be resolved by adopting legislation and thus fixing reflection on a given theme: this is the case for the issue of embryonic stem cells in France. 'No, No, that is not a discussion which interests me very much because I believe that it has been resolved […] and again no, no, the law on that question is related to the ethic of embryo.'[35]

From the interviews, it is quite clear that the manner of describing products deriving from nanobiotechnologies is more related to the mode of action of the product itself, to its future regulatory classification, than to discussions about ethics originating from regulatory bodies. The interaction between agencies and the biotech companies seems to operate a concrete transaction from ethical concerns to the definition of a shared accountability regarding biotechnologies.

Conclusion

The qualitative analysis complements and allows nuancing the quantitative treatment of the questionnaire by supplying context-sensitive details and sharper interpretations which quantitative analysis alone does not permit. Only the information obtained through direct interviews with industrial actors inform us as to how a tangible culture or a given organisation, or even the type of hopes for treatment in a given time 'have durably predefined' a specific 'ethical' manner of tackling the constitution of practices in time '$t + 1$'. The text data from the interviews thus gives indications concerning 'path dependency' (Liebowitz and Margolis, 1995, pp. 205–226) for producing ethics in the company with regard to its particular history. The notion of path dependency is used to express the idea that history matters—choices made in the past can affect the feasibility (possibility or cost) of choices that will be made in the future. This determination of the past is very strong as far as the activity of biobanking goes, as shown by one interview with the head of a company in France. As they grow, the first banks (particularly the first national bank) needed to adapt to the diversity of biological materials to be stored as well as to the disorders represented by these specimens. This widening of the types of biological samples led to the renegotiation of conditions of donation since the initial agreements with patients were drawn up with a restricted view as for the use (to be studied for a given disorder). To this end, the representatives of a patient association

were present when the regulations concerning bioethics were revised so that the consent to make a donation could be extended to a broader range of researches and uses of biological material. The aim was that all material arising from a donation contained in the bank might be able to be used for the wider research perspective. Today, the ethical procedures concerning confidentiality, the secondary use of specimen, and the data sharing, tend to come into line independently of the type of biological material in the bank. The means of producing good ethical practices is in line with a strong 'path dependency' of the initial organisational outline of the bank. It is also this bank, which was the first to obtain a national authorisation from the Biomedicine Agency in France to store human embryonic stem cells, thanks to the requirements for traceability that it had already established for other biological materials. This 'path dependency' is not therefore attached to the principle of therapeutic action but to the already established process of collecting and storing the specimen that is, in a particular infrastructure.

Another example, the framework procedures within the same country, can be quite different for processes, which are equivalent in terms of principle of action but distinct in terms of their material research culture and of their applicability to a given population. This is the case for example of by-products of embryonic stem cells (such as the precursors of mature cells, that is, cells in the process of differentiation) in France. Unlike products for cell therapy, where the guidelines are well set out in terms of regulation, the by-products of embryonic stem cells suffer from a regulatory vacuum, in particular concerning their circulation and transfer from one laboratory to another (Although research, storage and importation of human embryonic stem cells are regulated). The actors interviewed would like to see unification of these two regulations (cell therapies and embryonic stem cells) and a relaxing of the regulations covering clinical trials based on cell therapy products. Despite the similarities between therapeutic action, and the biological proximity between cell therapy products and differentiated products, which are by-products of embryonic stem cells, their production—and ethical issues attached to it—is not part of the same history of practices. This is relevant for the manner in which debate about ethics takes form and becomes part of the history of technical processes (Tournay, 2009, pp. 40–50).

Conversely, the production of ethical standards also reveals the manner in which scientists organise their research. For example, concerning Gaucher's disease, the important point for organising research on this orphan disease on a large scale, is that the patient or his/her authorised representative has given consent. This condition is a basis to set up a register which can be progressively extended: after treatment, the doctors write up their patients' results in the register, quarterly or annually, so as to combine them for this small group of patients, but worldwide it then becomes a larger group, and with wider results so that consequences can be drawn to improve clinical practice and the product and if necessary, the disease management. Establishing templates of consent or collective registers for orphan diseases, which initially involved only a small group of patients, on a large scale,

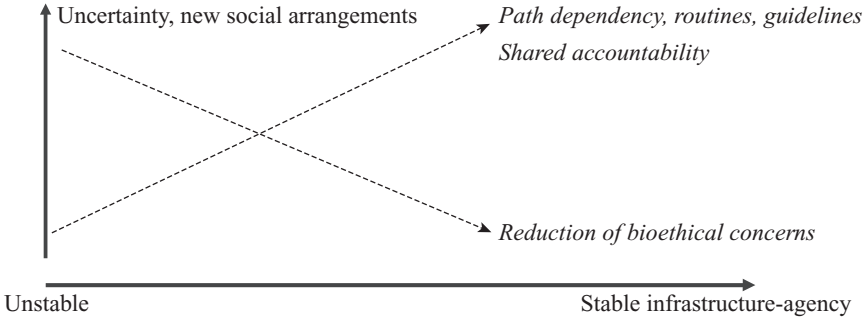
enables the initial sample to be widened and create a 'path dependency'. Good recommendations prescribed for clinical trials are a 'path dependency' offering favourable conditions for the implementation of multicentre protocols.

We highlight that ethical practices combined with industrial activity are rooted in the emerging technologies examined. They correspond to innovative practices, not necessarily in the sense of a recognised performance of the products considered but rather because they are the coherent result (Knorr-Cetina, 1981, pp. 33–93, 1999, pp. 26–45; Pickering, 1995, pp. 229–234) of a complex 'knocking-together' (Ciborra and Lanzarra, 1994, pp. 61–86). This knocking-together is both the product of a remarkable technical assemblage and an agreement between multiple actors (academics, patient associations, manufacturers) who have got together over a technological project (Granjou and Barbier, 2010, Introduction; Latour, 1989, pp. 59–70; Leibing and Tournay, 2010, pp. 3–46). The project dimension is at the heart of the very process of these innovations, which situates our study in line with the sociology of expectations (Nowotny and Felt, 1997: Introduction; Van Lente and Rip, 1998, 195–220). The latter claims a tight link between the constitution of hopes, the anticipation of action and the construction of material arrangements. The debate about bioethics reflects precisely this logic of *expectation* since this type of debate corresponds above all to an alert, bringing simultaneously fear and promise for mankind. In conclusion, the setting up of bioethical concerns is based on an already existing specific infrastructure which includes established processes of collecting, storing specimen and existing relationships within the company, rather than on an external judgement applied to objects, or a collection of processes of reasoning that are cut off from the rest of social discourses. This link between the production of ethical discourse and the progressive acquisition of a stabilised infrastructure is shown in the Figure 1.

Through this theoretical detour, we can see the importance of studying the debate about ethics as an element likely to contribute to the harmonisation of technical arrangements. Well before the products are technologically ready and certain in terms of prospects for treatment, all the related practices will be subject to some

Figure 1

Infrastructure Stability and Ethical Production



level of regulation by professionals or by public authorities. These actors place the concerns of society at the heart of their activity; many bioethical recommendations often go hand in hand with a regulation when it exists. The production of ethics then has practical effects in real time on the construction of the expectation of these new technologies, in terms of the production of good practice guides and supervision. These practical effects are comparable to 'Prospecting Retrospects' (Brown and Mike, 2003, pp. 3–18), heralding a future in the making. They are the support for concrete supervision of medical innovation. As we have seen, the aim of this study was not simply to propose solutions but also to develop a methodology specific to the understanding of ethical issues, and which will enable differences and tensions to be resolved between the scientific community and society. They may include anticipated risks and actual risks, hopes and fears. Considering the production of bioethical statements in close relation to researchers core work presupposes a focus on an ontological solidarity among social elements (linguistic, material). This differs from a 'vertical' approach of the power relationships. Hence an analysis of emerging industrial activities can lead to explore the horizontal dimension of collective experiences. Bioethics can be seen as a specific form of medical activism, which is directly correlated to the widespread politicisation of medicine and, more generally to the mutations in biopower (Rose, 2006, pp. 252–260). Therefore, our approach to ethical stakes appears as all the more essential to the future construction of policies adapted to such innovative products, and to the implementation of specific recommendations applicable to these new technologies.

NOTES

1. This expression refers to its use in anthropology and emphasises artefacts as a subject unto themselves. It does not echoe the technical aspect of 'cell culture' or 'biological material' used elsewhere in the fieldwork.
2. The authors distinguish four types of standards commonly found in health care: design, terminological, performance and procedural.
3. An initial sample of biotech companies was established with the aim of covering a wide range of production contexts and of different national regulatory situations. This was done with the help of the executive committee of this consortium, made up of European Academics and European Representatives of Industrial Partners.
4. Interview A, Manager R&D and Medical Affairs, Company of Gene therapy treatments, Paris, 15 March 2007.
5. Interview B, Scientific manager with a medical background, Stem Cell Research Company, Paris, 7 June 2007.
6. Interview C, Business function, Cell Therapy Company, Belgium, Bruxelles, 5 June 2007.
7. Interview D, Scientific manager with a physico-chimie background, Nanobiotech Company, Paris, 25 April 2007.
8. Interview C.
9. Interview E, Medical background, Nanobiotech and Clinical Trials Company, Paris, 25 April 2012.
10. Interview F, Managing director with a bio-industrial sciences training, Rare disease Company, Bruxelles, 6 June 2012.
11. Interview A.

12. Interview C.
13. Interview A.
14. Interview F.
15. Interview A.
16. Interview C
17. Interview B.
18. Interview F.
19. Interview G, Principal Scientist, biochemistry background, Stem Cell Company, Gothenburg, 8 June 2012.
20. Interview D.
21. Interview A.
22. Interview A.
23. Interview B.
24. Interview A.
25. Interview H, Head of Research R&D department, medical doctor, Diagnostics Company, Hungary, 13 June 2007.
26. Interview A.
27. Interview E.
28. Interview E.
29. Interview H.
30. Interview E.
31. Interview D.
32. Interview A.
33. Interview B.
34. Interview G.
35. Interview A.

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