

SIXTH FRAMEWORK PROGRAMME
PRIORITY: Structuring the European Research Area
SCIENCE AND SOCIETY



Contract for:

SPECIFIC TARGETED RESEARCH PROJECT (STREP)

From GMP to GBP
Report of GBP survey - WP 2, Final Version

Project acronym: **From GMP¹ to GBP**

Project full title: **From GMP to GBP: Fostering Good Bioethical Practices (GBP) among European Biotechnology Industry**

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¹ Good Manufacturing Practices

Contents

| | |
|--|----|
| Contents..... | 2 |
| 1 Project summary..... | 3 |
| 2 Place of WP2 in the general work plan..... | 4 |
| 3 Project Objectives Reminder for WP2..... | 5 |
| 4 The survey..... | 7 |
| 4.1 QUALITATIVE INTERVIEWS..... | 7 |
| 4.1.1 Identification of fields and companies..... | 7 |
| 4.1.2 Preparation of an interview grid..... | 7 |
| 4.1.3 Realization of the interviews..... | 8 |
| 4.1.4 Transcription of the interviews..... | 10 |
| 4.1.5 Analysis of content and identification of main trends..... | 10 |
| 4.1.5.1 Introductory data..... | 11 |
| 4.1.5.2 A huge variability of bioethics issues..... | 11 |
| 4.1.5.3 How private stakeholders give answer to bioethics concerns?..... | 12 |
| 4.1.6 Presentation of the analysis to the Scientific Committee..... | 12 |
| 4.1.7 In depth analysis of the qualitative survey's results for an article submission .. | 13 |
| 4.1.7.1 The problem and the introduction of a methodology..... | 13 |
| 4.1.7.2 Construction of qualitative analysis..... | 14 |
| 4.1.7.3 Constitution of an initial sample of biotech companies and drawing up the questionnaire..... | 18 |
| 4.1.7.4 The focus for analysis of the interviews..... | 18 |
| 4.1.7.5 Identification of bioethical questions by the actors themselves and production of ethics within the companies..... | 18 |
| 4.1.7.6 Means of resolving ethical questions by resorting to external agencies..... | 27 |
| 4.2 QUANTITATIVE SURVEY AND COMPLEMENTARY DATA..... | 35 |
| 4.2.1 Elaboration of the questionnaire..... | 35 |
| 4.2.1.1 From qualitative interviews to the questionnaire..... | 35 |
| 4.2.1.2 Iteration of the questionnaire within the steering committee and scientific committee..... | 36 |
| 4.2.1.3 Mounting of the questionnaire in an on line tool and testing it for operability..... | 37 |
| 4.2.1.4 Construction of the sample among European biotech companies, methodology and sending the information to this sample through the national associations..... | 38 |
| 4.2.1.5 Gathering results and analysis..... | 38 |
| 5 Conclusion..... | 48 |
| 6 APPENDIX..... | 49 |

1 Project summary

The Project aims at improving understanding of bioethical issues by using the daily practice of biotechnology companies, to elaborate clear and independent positions based on regularly updated scientific and technological data. It will also contribute to include industry into the dialogue with the largest audiences and to help the dissemination of information both to industry and other groups of society.

The Project involves biotechnology companies from Estonia, Hungary, Spain, together with Sweden, and France, which is the initiator of the Project, through the participation of their National Associations, and more generally companies from all over Europe, through Europabio participation. A very important partner is INSERM which plays a pivotal role in being an interface with public research and with ethic bodies.

In this way, the project will privilege a multi-cultural approach of biomedical research and its applications, enriched by the increasing involvement of the new European states in the biomedical research and their necessity to catch up with European standards.

Biotechnology companies understand that their usual responsibility to elaborate and anticipate the implications and possible impacts of their practices have to be shared and confronted with the very actors of these changes. They should bring to society their own questions about the productions in their labs. They should not only propose this questioning, but mainly listen, confront and get new approaches to new questions that should not have popped out from their day-to-day practice, and that society could consider important or crucial to our common developments.

The Project addresses three Strategic Objectives:

- **Improve understanding of bioethical issues, using the daily practice of biotechnology companies**
- **Facilitate the participation of the biotechnology industry in the definition of bioethical policies and recommendations**
- **Construct a methodology for a multi-cultural approach of biomedical research and its applications**

The main aim of this programme is not only to propose solutions, but to develop a **methodology** of approaching ethical issues, mainly bioethics, in order to improve understanding and to develop recommendations. This methodology would apply to European companies and to Society in order to tackle the gaps and discrepancies that widen between science and society, between risk and perceived risk, between expected hopes and anticipated fears.

2 Place of WP2 in the general work plan

The implementation plan for this programme is built on the networks of the national biotechnology associations participating and their mobilisation capacity in order to:

- i) **Survey** the state-of-the-art in terms of bioethics practices among the industry
- ii) **Benchmark** the results and identify key-emerging issues
- iii) **Promote bioethics studies** and knowledge, exchanges of results and of good practices among companies
- iv) **Promote exchanges** with other stakeholders, academic researchers and clinicians, patients

The goal is to integrate bioethics practices as an intrinsic part of the industrial R&D standards, just as are the Good Clinical Practices (GCP) or Good Manufacturing Practices (GMP). These Good Bioethical Practices (GBP) standards could in return allow the industry to define its own perspective and make it eligible and welcome to the public debate.

The Programme is planned according to the following “workpackages”:

- WP1 : Management of the project

(overall contractual, legal, ethical, financial management and coordination)

- WP 2 : Industry Survey and State of the art Status

(daily bioethical practices of a targeted group of European biotechnology companies)

- WP 3 : Presentation of results. Workshops and Conference 1

(organisation of reflection seminars with experts, regulatory agencies and policy-makers, patient organisations in the different countries involved in the project)

- WP 4 : Implementation of an Observatory of Good Bioethical Practices

(structure and status of the Observatory, Guidelines and recommendations)

- WP 5 : Dissemination of guidelines and recommendations

(recommendations to policy makers, national workshops for dissemination and position papers)

- WP 6 : Stakeholders meetings, Conference 2 and White Paper

(preparation of the second GBP conference by the Observatory of GBP and Publication of a White Paper following the conference findings)

The first expected result of this programme is a **better understanding of daily bioethical practices and emerging issues on up to date questions within the European biotechnology industry.**

WP2 is contributing to this objective through a direct exploration of various practices in relevant companies. This final version of D1 is giving the results of all tasks related to the

survey: task 2.1 “Qualitative analysis & Overall Preparation”, task 2.2: Study on national bioethical practices and task 2.3 Analysis, reports, and Preparation of dissemination

3 Project Objectives Reminder for WP2

Objectives

Presentation of results and organisation of seminars with experts

Draw a clear picture of the impact on bioethics of the actual daily Research and Development practices: informed consent and its modalities, procedures established for the disclosure of clinical trials, biobanking and human bioresources, privacy protection and traceability procedures, interaction with Ethics Committees, interactions with regulating agencies, emerging issues in approval procedures in clinical trials, especially in new European countries

The specificity of this project is not only to propose recommendations from various institutions but to picture, from the practices, some relevant proposals in bioethics. This “bottom-up” approach is based on the hypothesis that a gap exists between the existing corpus in bioethics and companies’ practices. The scientific goal of the project is to document this gap, to understand its reasons and to propose some concrete solutions to allow the practices to meet bioethics requirements. To achieve this objective, mapping the different issues regarding the biotech companies’ practices in bioethics, we identified two tasks:

- First, the relevant companies had to be interviewed during this phase of the project: qualitative interviews (step 1). The different associations involved in the project as partners were of invaluable help in this step as the adequate identification of informative companies was essential. This important phase is described below and is of high value for the next step.

- Second, quantitative analyses of an extensive and relevant questionnaire based on step 1 results (step 2) have been performed and presented and discussed at the first conference in December 2007, according to a change in the work plan as described in the next paragraph.

During the beginning of the project we faced difficulties to perform the methodology as planned, which, induced some delays. To face these delays the Executive Committee held on 24th of April 2007 decided a methodological switch in the way the input for reflexion (survey, consultations) would be gathered. It was decided to encourage the Partners to organise the national workshops according to the plan and under a list of proposal themes from France Biotech. For WP2 it was decided to pursue the task and that the totality of the survey plus the national workshops would constitute the input for the Conference 1 to be held in December 2007. The present deliverable takes into account input from the Conference about the results.

A methodology was set up as follows:

- Qualitative study
 - 1) Identification of fields and companies
 - 2) Preparation of an interview grid
 - 3) Realization of the interviews
 - 4) Transcription of the interviews
 - 5) Analysis of content and identification of main trends

- 6) Presentation of the analysis to the scientific committee and identification of elements to include in the questionnaire
- 7) Redaction of the results for an article in a social science journal
 - Quantitative study and, if necessary, complementary interviews
- 1) Conception of the questionnaire
- 2) Iteration of the questionnaire within the steering committee and scientific committee
- 3) Mounting of the questionnaire in an on line tool and testing it for operationality
- 4) Sending the information to companies through the national associations
- 5) Gathering of the results and analysis
- 6) Presentation of the results and discussion in First Conference
- 7) Complementary interviews if necessary
- 8) Redaction of the results and synthetic article for a biotechnology journal.

4 The survey

4.1 Qualitative interviews

The above described methodology led to the following steps.

4.1.1 Identification of fields and companies

Thanks to the interactions between partners, 5 fields of prominent activities were identified, that were specifically relevant for the project: stem cell research, gene and cell therapy, nanobiotechnology, biobanks, diagnostics (see appendix 1).

Semi-directive interviews were performed with the Chief Executive Officers (CEO) of the biotech companies selected.

The companies were identified through their national associations on the following criteria:

- To be active in at least one of the fields selected (the 5 fields had to be represented)
- To be distributed over the various countries involved
- To represent various levels of involvement in bioethical approaches
- To show willingness to deepen their approach on the ethical aspects of their activity
- To accept a recorded interview.

Among 20 companies that underwent the first selection, 14 were finally contacted (see Appendix 1).

The calendar of interviews was completed with the help of associations and appointments were set up by Inserm and France Biotech over 4 months (March to June 2007).

4.1.2 Preparation of an interview grid

A working group was set up to complete this task; it included, a sociologist, a political scientist, a jurist, two members of different ethics committees, a researcher (MD), an industrial member of France Biotech.

The following issues were pinpointed:

- patient information and consent request practices
- establishment of working routines with organised patient groups
- procedures established for the disclosure of clinical trials results
- banking practices ; human body parts conservation and traceability procedures
- interaction with Ethics Committees
- interactions with regulatory agencies

- emerging issues in clinical trials procedures, especially in new European countries
- and other relevant issues.

Following this work and discussions an interview grid has been finalized (See Appendix 2). The interview was structured in 5 items:

- History of professional trajectories and organisational characteristics of companies
- Characteristics of technical processes setting within companies
- Conditions of bioethical issues within companies
- Pragmatic features of bioethical issues within companies
- Elaboration of standards of practice guidelines

4.1.3 Realization of the interviews

The main paragraph of the e-mail for contacting selected companies to solicit an interview, in addition to presentation of the persons involved, is reproduced below:

Example of a French version contact for company working in the domain of nanotechnologies and clinical trials:

« Je vous contacte dans le cadre du projet européen n°036806 coordonné par France Biotech et intitulé "Fostering bioethics practices (GBP) among the European biotechnology Industry". Emmanuelle Rial coordonne ce volet du projet. L'objectif est de restituer les enjeux bioéthiques autour des produits de l'innovation à partir des pratiques concrètes des entreprises de biotechnologie afin de faciliter la participation de ces acteurs dans la définition des recommandations éthiques et des politiques associées (résumé ci-dessous).

Dans cette optique, je souhaiterais vous interviewer pour comprendre les questionnements particuliers à votre activité (nanobiotechnologies et essais cliniques). Est-il possible de nous rencontrer ? Je suis justement de passage à Paris dans ces prochains jours. »

“The Project aims at improving understanding of bioethical issues by using the daily practice of biotechnology companies, to elaborate clear and independent positions based on regularly updated scientific and technological data. It will also contribute to include industry into the dialogue with the largest audience and to help the dissemination of information both to industry and society. The Project involves biotechnology companies from Estonia, Hungary, Spain, together with Sweden, and France, which is the initiator of the Project, through the participation of their National Associations, and more generally companies from all over Europe, through Europabio participation. A very important partner is INSERM which plays a pivotal role in being an interface with public research and with ethic bodies. The main aim of this program is not only to propose solutions, but to develop a methodology of approaching ethic issues, mainly bioethics, in order to improve understanding and to develop recommendations.”

Example of an English version contact for company working in the domain of nanotechnologies and clinical trials:

“The GMP to GBP project, number 036806 which is included in 6th Framework Program is a project which **aims at improving understanding of bioethical issues by using the daily**

practice of biotechnology companies, to elaborate clear and independent positions based on regularly updated scientific and technological data. It will also contribute to include industry into the dialogue with the largest audiences and to help the dissemination of information both to industry and society.

The project involves biotechnology companies from Estonia, Hungary, Spain, together with Sweden, and France, which is the initiator of the Project, through the participation of their National Associations, and more generally companies from all over Europe, through Europabio participation. An important partner is INSERM which plays a pivotal role in being an interface with public research and with ethic bodies.

Description of the survey

Each national biotech association usually has a clear picture of the general bioethical questions which arise in its affiliated biotechnology laboratories. However, no homogeneous picture of these bioethical questions **in the labs** has ever been made at the European level. Moreover, these questions only pop-out an organised way during special meetings and conferences usually organised at the national levels.

The survey will be organised to check **how a biotechnology laboratory copes with the difference between the timing of the scientific and innovative process and the one of the society understanding and approval**. Questions about the implementation of individual code of ethics will be checked.

To prepare the survey performed by INSERM, a first qualitative analysis will be set-up. Semi-directive interviews will be performed with the Chief Executive Officers (CEO) of the biotech companies of the 3 fields of activities on which the project will focus:

- Companies sponsoring ongoing **clinical trials** for questions about consent of patients,
- Companies developing **cell and gene therapies**, as well as performing **stem cell research**,
- Companies integrating **nanotechnologies** in the biomedical research, with a specific focus on neurosciences.
- **Biobanks**
- Companies developing **diagnostics**

These companies will be identified through their national associations and will be **questioned on the following issues**:

- patient information and consent request practices
- establishment of working routines with organised patient groups
- procedures established for the disclosure of clinical trials results
- banking practices; human body parts conservation and traceability procedures
- interaction with Ethics Committees
- interactions with regulatory agencies
- emerging issues in clinical trials procedures, especially in new European countries
- other relevant issues.

The second part of the project will be the quantitative survey, which focuses on around 80 biotechnology companies all over Europe.

Return to participants

The survey results will be presented at the end of 2007 during a national conference organised by SwedenBio.

An Observatory of GBP (OGBP) presented via a website is planned to gather several information, to make them widely available, that is:

- Regulatory overview of different countries involved
- Results of the survey: qualitative and quantitative part
- Results of the National Workshops of each country
- Summaries of the conferences 1 and 2
- White paper

As specialists of biotechnological and bioethics issues, we would like to suggest you to take part actively on this European project and we would be very happy to involve you.

For any questions, please feel free to contact your national association”

Interviews were performed by:

- 1) Virginie Tournay, PhD in biology and political sciences, researcher at CNRS (Grenoble), who was selected by Inserm because of her experience in theoretical and field work in political sciences in an international context, dealing especially with bioethics practices;
- 2) Emmanuelle Rial-Sebbag, jurist at Inserm, researcher in biolaw and health law, Toulouse, experienced in ethics and legal framework for biomedical research, biobanks and innovative therapies.

Each face to face interview lasted about 1 to 1.5 hours and was recorded (with permission). The anonymity for the transcription and the use of the content of the interviews was guaranteed to interviewees.

4.1.4 Transcription of the interviews

For the transcription we identified 2 professional persons (One in France and one in England). Half a week is necessary for the transcription and return of each individual interview.

The methodology insists on the exact transcription of the interviews. The content of these transcriptions has been used for the sociological analysis mentioned below in addition to elements collected in the vocal files. The retranscriptions were transferred for archiving to the Coordinator of the project and will not be distributed, in order to respect fully the anonymity of the Companies.

4.1.5 Analysis of content and identification of main trends

The analysis focused on the following issues:

4.1.5.1 Introductory data

First interviews made on conditions of bioethical issues appearance within companies show that, for industrial stakeholders, ethics is neither a simple judgement applied to objects, nor is it a collection of reasoning processes that are isolated from the rest of industrial activities. Bioethics concerns are a means of describing the conditions under which the innovative medical (or biotechnical) practice became possible. More especially, ethics concerns describe the interface between an emerging medical technique and the public (or private) instrument that would control it. This is particularly true for medical uses involving human body elements such as cell therapy, embryonic stem cell research, diagnostic testing. Bioethical concerns help in assigning a medical label to technologies that exist in the form of projects developed from laboratory practices (such as gene therapy, hESC or therapeutics based on nanobiotechnology products).

4.1.5.2 A huge variability of bioethics issues

Because bioethics regulation is inextricably linked to the scientific work context and to the anticipated political regulation of emerging medical techniques, their appearance and implementation within the history of companies are conditional on each specific local context. Some factors act in favour of the development of bioethical issues within companies:

- The presence of patient groups in the beginning of the company
- The company strategy to develop activities on a large scale with different human elements (in order to legally protect company activities and to improve collaborations between heterogeneous actors)
- The integration of each innovating step within the companies. If conception, fabrication of products and clinical trials are brought together within the company (with less subcontracting innovating process activities), bioethical concerns are stronger.
- The innovating grade of the process (more important than therapeutic properties of the innovating product)
 - If the innovating process is closely related to clinical trials or medical expectations, bioethics issues arise (For instance, it is not therapeutic effectiveness that defines the practices included under the “cell therapy” label, but rather the various ways in which human cell products are obtained before being injected to patients). So, characteristics of technical processes are more important than concrete therapeutic properties as far as construction of bioethics issues is concerned.
 - If the technology is an experimental device with few links with current medical activities but related to high level of public expectation, bioethics concerns are stronger.
 - If the technology corresponds to working routines in the manufacturing process, bioethics issues tend to disappear (biobanking, techniques for obtaining human cell products in regular medical practice in the process of being standardized ...)
- The therapeutic action of the drug developed within a company (or legally recognised). If the product is assimilated to a medical device (a nano-biotechnology

that can be activated by external agents, such as X rays for instance), bioethics concerns are completely different from situations where the products are considered as biological drugs.

4.1.5.3 How private stakeholders give answer to bioethics concerns?

Bioethics issues allow private companies to create a link between disjoined universes such as legal and medical ones. This takes various concrete forms so that each one could be considered as political standards that have pragmatic effects on the shaping of the innovating process:

- Communications and spreading of information to patient groups and hospitals.
- The widespread use of medical guidelines. For example, some companies develop their proper consent forms since the beginning of their activities. Its signature by the donor of biological elements is a necessary constraint to recognize biological elements as entities that can serve as (or be integrated in) a technical device.
- For the medical use of human elements, we notice the important role that overarching ethical principles play in the qualification of the various components of the human body – tissues and cells, and in the constitution of pragmatic constraints in the process of obtaining biological products. For instance, the act of “donation” is based on three conditions: the donor consenting, the prohibition against buying and selling human element donation and the confidentiality in data-gathering and their management. This constituted a practical constraint by which human cells became unquestionably technical, materially and symbolically removed from the native body. Then, applying this moral principle has specific pragmatic effects, including the implementation of a prior consent form for donors.
- Some answers come from top-down regulations or bottom-up ones. In France, the regulation of the medical use of human cells and the associated knowledge is now the exclusive domain of regulatory processes implemented by health agencies. But, in Sweden, private companies develop their own standardized regulating practices based on specific ethics statements.
- The promotion of a medical product through the media is not a consequence but a condition for private companies for obtaining funds. So, bioethics concerns are often directly integrated in companies’ projects for developing medical innovating products (notably in the case of capital venture companies).

Bioethics issues seem inextricable from industrial implementation in biotechnologies and standardization of the manufacturing process of products (biological drugs and medical devices). The more medical knowledge and practices are stabilised, the more ethical concerns tend to disappear.

4.1.6 Presentation of the analysis to the Scientific Committee

During early July 2007 Virginie Tournay, Emmanuelle Rial-Sebbag and Anne Cambon-Thomsen prepared an analysis of the 10 interviews done for the qualitative survey in order to construct the questionnaire for the quantitative survey. After analysis of the interviews, a first draft of the questionnaire was designed as self administrated questionnaire with a maximum

of closed questions; it was worked out in English and subsequently possibly adapted or commented in each country language. The analysis and the questionnaire were submitted to the scientific committee the 10th of July 2007 to be discussed, commented and amended. The adoption of the questionnaire would engage the project into the next phase consisting in a quantitative survey (see below in quantitative study after the detailed analysis of the qualitative study).

4.1.7 In depth analysis of the qualitative survey's results for an article submission

4.1.7.1 The problem and the introduction of a methodology

The aim of this study is to examine the way in which bioethical concerns take shape and develop in private biotech companies. A comparative analysis was undertaken in various European countries in companies working on a wide range of emerging technologies which use human materials (diagnostics from human tissues, nanobiotechnologies, storage and preparation of cell therapy products, research based on embryonic stem cells) or including human beings (clinical trials). This study was carried out in five different countries: France, Italy, Sweden, Hungary and Belgium. Semi-structured interviews were carried out with heads of companies to see how industrial actors take on board existing ethical recommendations or are brought around to producing standards themselves to regulate their own practices. The aim of this technique of collecting data is to focus on the statements of those interviewed on the various themes that we had previously defined. To this end, many follow up requests, and requests for more details made in the communication between interviewer and interviewee were necessary to be able to build up the textual data which can then be used for research purposes. These interviews are a representative sample of all production contexts and of the countries involved in the study. The corpus of texts of the retranscriptions arising from the interviews has been used with a two-fold purpose:

- To draw up a more general questionnaire to be sent to a much wider group of companies (sixty to eighty were targeted). 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. It is a question of checking whether the elements obtained during the interviews for each biotech sector are representative, and of determining what stands out as the decisive ethical standards for the sectors of activity studied, and then to distinguish the more anecdotal elements from those more specific to a given company.

- To conduct in parallel a qualitative analysis, the aim of which is to discuss in even greater detail the nature and importance of the reflections produced concerning ethics, involving the emerging technologies in relation to the country under consideration, and the particular nature of each of the technologies considered. By not initially imposing a framework of understanding, the interviews bring in circumstantial elements. An analysis of the contents was carried out based on a framework of reference and compared to the contents of the interview (Interview Guide - Appendix 2). We then had to pin point the elements of the interview grid used. This analysis rounds out the quantitative treatment of the questionnaire by supplying context-sensitive details and sharper interpretations which quantitative analysis alone does not permit.

The whole of this survey is above all an exploratory study with the aim of informing the consortium and the European Commission of the needs and wishes of companies in relation to the making of documentary resources and the providing of an observatory of good practices in bioethics. The aim is therefore not simply to propose solutions but also to develop a methodology specific to questions of ethics which will enable differences and tensions all round to be resolved between the scientific community and society, differences concerning anticipated risks and actual risks, hopes and fears.

4.1.7.2 Construction of qualitative analysis

The framework of reference for this interview work was defined so as to not influence the responses and therefore contains as little *a priori* as possible in the manner of designating what the term "bioethics" covers and no indications too specific concerning legal tools or historical reminders which could be seized upon by the interviewees. This framework also includes questions concerning emerging contexts, organizational features and fields of expertise of biotech companies.

Five main themes have thus been predefined:

- History of professional trajectories and organisational characteristics of companies;
- Characteristics of technical processes setting within companies;
- Conditions of bioethical issues within companies;
- Pragmatic features of bioethical issues within companies;
- Elaboration of guidelines for standards of practice.

Initial interviews carried out concerning the appearance 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 other 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. Firstly, 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 ?* ». Then, the type of ethical rules and regulations described by the actors is strongly attached to the emergence of biotechnologies in a specifically national context (in particular to the type of production), which reflects 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 is much smaller.*” Lastly, despite the diversity of context, the term “ethics” is more frequently associated with certain words or groups of words in the corpus of texts, such as: “patients,” “clinical trials,” “embryonic,” “consent,” “communication,” “information,” etc. It is a term which is not spontaneously used as various actors interviewed underlined: “*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.*” We can see here the interest of studying local discussions about ethics which emanate directly from the production sites to draw up a research methodology around these questions which are difficult to grasp. By paying particular attention to each local scene, the bottom-up approach directly questions the link between good ethical practices and the actual degree of progress in the technology under consideration. Unlike the production of recommendations for institutions which place 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 automation of the technical process. 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. The analysis of the ethical stakes following this type of approach is therefore an element all the more essential to the future construction of policies adapted to these innovative products and therefore to the implementation of specific recommendations applicable to these new technologies. This does not exclude taking the professional track and specific expertise of the people interviewed into account 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 hopes of the patient (many

have based their project on therapies applicable to rare and lethal diseases) than the corpus obtained from the biologists interviewed, whose aim was to provide guarantees concerning the construction of ethics involving a technical process.

Interview with a business manager who has a medical background: *“The whole problem with the embryonic solution, 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.”*

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.”*

Table 1. Details concerning companies interviewed

| Fields of activity | Country | Year founded | Employed Persons | Fields of expertise | Technical devices | | Organisational specificities | |
|-------------------------------|---------|---------------------|---|--|---|---|--|---|
| | | | | | Raw biological materials | Research objectives | Ties institutions | Company in direct contact with patients studied |
| Clinical Trial Nanobiotech | France | 2001 Celogos | 20 persons | Clinical development, business development | Autologous and allogeneic sources of stem cells | Muscle regeneration Clinical trials | Pharmaceutical and biotechnology companies | Yes |
| Nanobiotech | France | 1998 Nanobiotix | | | Nanobiodrug | Cancer treatments Clinical Trials | | Yes |
| Stem Cells | France | 1996 Bioalliance | 60 persons | Clinical development of HIV medications | Chemical polymers and nanoparticles | Drug delivery Clinical trials | | Yes |
| Biobank | France | 1992 Genethon | 200 persons whose 40 in research areas | Storage, culture | Different kinds of biological samples | Storage of samples | | No (for this field of activity) |
| Cell Therapy | Spain | 2004 Cellerix | | | Allogeneic products and biomaterials | Clinical trials | | Yes |
| Cell Therapy | Belgium | 1981 Genzyme | 9000 persons | | | Clinical trials on orphan diseases | | Yes |
| Stem Cells | Belgium | 2000 Tigénix | 46 persons with 16 of them in Research area | Rheumatologists, Bioengineers | Autologous cell lines of cartilage, bone and connective tissues | Clinical trials for cartilage damage and joint disorders “ChondroCelect” | | Yes Trauma patient groups |
| Stem Cells | Sweden | 2001 Cellartis | 40 persons | Academics and Hospitals | 30 hESC lines | Xeno-free hESC medium Testing drug differentiated lines Scaling-up | | No |
| Diagnostics | Hungary | 2001 GenoID | | | Numerous biological samples | STD diagnostic tests based on PCR High automatization | Research and diagnostic Services | Yes Patient groups |

4.1.7.3 Constitution of an initial sample of biotech companies and drawing up the questionnaire

An initial sample of biotech companies was suggested by the partners (Executive Committee) with the aim of covering a wide range of production contexts and of different national regulatory situations. From this initial crop and from the heads of companies available for the survey, the sample was constituted (Appendix 1).

4.1.7.4 The focus for analysis of the interviews

The framework of reference for this interview work was defined so as to not influence the responses and therefore contains as little *a priori* as possible in the manner of designating what the term "bioethics" covers and no indications too specific concerning legal tools or historical reminders which could be seized upon by the interviewees

The selection of companies thus made, offered certain comparable traits so as to be able to follow the production of ethics in the companies selected. The responses to the interviews were grouped into two sets enabling careful analysis and the drawing up of the quantitative 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 implementing solutions into concrete practices (3.1.7.5). 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. (3.1.7.6)

4.1.7.5 Identification of bioethical questions by the actors themselves and production of ethics within the companies.

4.1.7.5.1 bioethical questions identified by actors

The various actors expressed in different ways the bioethical questions which they might have to deal with and specified the context in which they came to the fore (medical discussion, respecting quality standards, etc.).

The corpus obtained from interviewees with a medical background was more centred on the hopes of the patient (many have based their project on therapies applicable to rare and lethal diseases) than the corpus obtained from the biologists interviewed, whose aim was to provide

guarantees concerning the construction of ethics involving a technical process. Two samples of interview show this orientation based on the initial training.

First, with a business manager who has a medical background:

“The whole problem with the embryonic solution, is going exactly as it did for gene therapy, the problem of the stem cell which become 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.”

Second, 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.”

The following factors come into play in the structuring of bioethical concerns:

1. Description of conditions and pragmatic features of bioethical issues within the companies

Initial interviews carried out concerning the appearance 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. Firstly, 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?”

Actually, it is a term which is not spontaneously used as various actors interviewed underlined:

“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.”

Then, the type of ethical rules and regulations described by the actors is strongly attached to the emergence of biotechnologies in a specifically national context (in particular to the type of production), which reflects 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 is much smaller.”

Lastly, despite the diversity of context, the term “ethics” is more frequently associated with certain words or groups of words in the corpus of texts, such as: “patients,” “clinical trials,” “embryonic,” “consent,” “communication,” and “information”. The notions of communication and information occur in the constitution of a collective ethics for the people interviewed at various levels. Indeed, 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, from the research community through to the patient and to the public sphere. They are found in the properties of products currently in preparation:

“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.”

4.1.7.5.2 some ethical standards for technical devices?

1. **The level of automation of practices.** The interviews concerned the emerging technologies more (production of diagnostic kits for genetic disorders and infectious diseases) or less (nanobiotechnologies) defined in terms of processes/methods. In the first case, it was a question of improving existing automated processes in order to accelerate screening procedures, to improve the sensitivity of this detection, then to extend it to the tests for candidate molecules. In the second case, the industrial challenge lies in turning this 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, robotized test systems on a large scale, etc.) which are well-known today and found throughout research laboratories and in pharmaceutical companies.

2. **Construction of an ethics and diversity of biological samples.** One of the interviews carried out concerned a company storing a wide diversity of biological samples. There was a lot of tension between the production of common ethical recommendations and the diversity of procedures for managing the specimen. It is interesting to see the way in which the standards for consent are negotiated according to the type of biological element and the arrival of new treatment projects. In addition, the ethical questions which emerge, in particular when the companies store or use cell lines (embryonic or not) are in the majority related to the use of such cells, to questions concerning the embryo, to the marketing and to the original properties of these cells, e.g. *“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 people who are sources of material and their data: *“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 capital...”*

3. **Regarding the value of collections of biological material**

The interviews showed a diversity of situations in relation to the banking of biological material. As we underlined above, the nature of the products stored strongly influences the bioethical concerns raised within the companies. This diversity of situations is correlated to how the "bank" is organized within the company. Some interviewees link the story of their organization to the early establishment of a biobank as a resource for the development of subsequent activities: *“We were the first laboratory, the first DNA bank in France, existing, and we received a huge amount of samples”* (this high degree of organization can be linked to the fact that the biobank was initially set up for a serious, rare disorder). Whereas the establishment of a centre for storing biological material can follow on from the activity of the firm. It was when developing a technique that some manufacturers harvested specimen 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.”* The regulatory aspects and bringing the laboratory into line with the law are often mentioned as being the driving force behind the acknowledgement

of a biobank: if its value to research is recognized (*“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*).

4. **Production of ethical standards according to the links formed directly between patients and the company.** The sample selected includes 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). In the latter case, ethical concerns are marginal, they are rather described as quality control for the by-products of biological material, and as there being a requirement for international harmonization regarding these products.
5. **Production of ethics and method of administration of the innovative product.** The way in which the product must be administered to the patient influences what the actors describe as being the pin-pointing or triggering event of an ethical issue. 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 ? “*
6. **Production of ethics, quality control and therapeutic characteristics of product.** 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 classic standards of care or to inactive treatments ? The answer to this question differs 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 injection remains indistinguishable from the properties of a good medicinal product. Although intervening at the end of the clinical trial line, this type of concern directly concerns the company which has to prepare

the best it can these cell therapy products to limit discussions to the use of the injection: “*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.*” 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, can we refuse a patient if the quality is not optimal.*”

7. **Production of ethics and seriousness of the disease for which the innovative treatment may be the answer.** The sample of companies interviewed included cases of companies 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 expectancy of six months*” and “*And there is no other treatment for these patients. To not do it is already a problem.*”

4.1.7.5.3 *producing ethics within the companies: a variability of reference texts and arena involved*

- **The variability of reference texts involved in producing ethics in companies**

The references mentioned as being “sources for ethics” are very variable, ranging from restrictive legal instruments (laws, directives) to professional recommendations (FDA, Guidelines, the bioethics group of Europabio, etc.). It should be noted that only two structures 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 introduced 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.*”

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.”*).

Second type of scenario: there is no law: that particular sector of activity is in a type of regulatory vacuum and the regulatory institution is canvassed, then often seen as being a partner in order to adopt restrictive regulations. A company may also internally develop means of resolving conflicts over 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 »*.

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 harmonization they are supposed to produce (e.g. within the framework of the cell directive). The reasons mentioned are either that all the Member States have not transposed the provisions of the directives into their domestic law, or that transposition is differently completed in each State.

- **The place of communication and consent processes in the production of ethics**

As already underlined, the corpus of texts obtained shows that communication and information occur in the constitution of a collective ethics for the people interviewed at various levels. Indeed, if communication is envisaged as generating a flow of information towards the public in the widest sense (including care centres, health professionals, 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 to comply with informed consent. These two notions are thus present throughout the process of manufacturing a product for innovative treatment, and bring into play a diversity of actors, from the research community through to the patient and to the public sphere. They can be found, for instance in:

- Establishing consent:

“We will always be working with the consent² 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”

- Immediate communication with the patient, as the geneticists told:

“You have to speak to the patients. So I did, and now all those who were in this proactive context, at the beginning of the 1990’s, are now the major players on the side of the patients at the European level.”

- Meaning of the consent according actors interviewed

The meaning 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 meaning described by the actors interviewed as to the function of patient consent differs 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.”

In the case of donation for diagnostic purposes, informed consent enables people to carry out the research, without a clinical responsibility towards the patients.

“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!”

² In that case, consent was used to mean approval by the ethics committee

The meaning 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 eventuality, the re-injection of the product falls within 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.”

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.”

- Ethics is also a means of communication with the public too. In this case, the need to communicate is found in the actual organization of the company. This necessity may be formalized by the presence of a person in charge of communication, or by the existence of a commercial network (communication marketing) attached to the company.

- **Design of trials and production of ethics.**

Some actors allude 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.”* This refers to the implication of the actors who are involved in the technical procedure under consideration. In the example above, it is notably the organization of trials based on autologous elements which is compared to those based on allogeneic elements. Obtaining consent is registered 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.

- **Physical representation of an area for ethics in companies**

The ethical requirements once identified in a company are then pooled inside the structure itself in various forms which are more or less structured. Globally, these arenas for discussion are not very formalized, with perhaps the exception of the ethics of practices as applied to animal

experimentation where there will be a specific committee inside the company to deal with this question. 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: « *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.* »

4.1.7.6 Means of resolving ethical questions by resorting to external agencies

The notion of ethical responsibility

Although a majority of the actors felt concerned by the question of internalising bioethical questions, in relation to the specific activities of the company, the way in which the actors attempt to answer these concerns varies significantly from one industrial context to another. The notion of *ethical responsibility* is very present; it was materialized in the actors interviewed by the need to search for external opinion in order to find ready-made solutions (the question is asked internally and the solution is sought externally), or in order to confirm an opinion given internally (the question is asked internally, a solution is given internally and is corroborated externally: “*You have to have your own answer and you then need to have external confirmation.*”). The means of resolving the problem adopted by the actors faced with their ethical concerns thus imply the appropriation of a reference framework external to their practices.

1. **National regulatory bodies.** The presence (France) or not (Sweden) of regulatory agencies having a regulative role in a given jurisdiction, applicable to a given type of research practices: research using human embryonic stem cells is correlated with different attitudes. One of the important ethical issues for all the European companies interviewed who 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 contrasts strongly with the French regulatory framework since there are no national agencies applying regulations on human embryonic biological material. The research related to this type of material in Sweden was framed internally very early on 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:

- collaboration concerning the adoption (if there was a deficiency), or the adaptation of the regulations in the sector of activity. Regulation by rule of law is never envisaged as a constraint, but on the contrary 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.”*

- Collaboration concerning the products. Regulatory input occurs principally at two levels:

1. Upstream for classification of product. The interface between agency and 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 such as those involving nanotechnologies: *“These products internally regulated 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.”*

2. For determination of price:

“Interviewer: Take AFSSAPS³, 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: Yes, licensing.

[...]

Interviewer: The procedure part. And HAS⁴, that’s ...

Interviewee: The price !”

2. The rule of law as a means of resolving ethical questions

³ AFSSAPS: Agence française de sécurité sanitaire des aliments et des produits de santé

⁴ HAS : Haute autorité de santé

The actors often mention the compliance of their practices with legal standards. This observation is an active part of finding a consensus of opinion, in resolving their bioethical questions. Thus, complying with a law, for example in the field of clinical trials, means that questions concerning information and consent of the participant in the study can be resolved. Law and reflections concerning ethics are thus often mixed in what the actors say and, even more so, their function for the company is judged to be equivalent. But the rule of law has the advantage of constraining force whereas recommendations 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 !”*

Another major aspect is the fact that 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 from the bodies concerned. This can be interpreted as allowing questions concerning ethics to be resolved by adopting legislation and thus fix reflection on one theme: For example regarding the subject 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 the ethic.”*

3. **The susceptibility of industrial actors to formalized bioethics.** This analysis covers a corpus of two interviews carried out in French biotech companies working on nanotechnologies. The "nano" label reflects practices where the definition, the outline of the disciplines involved, the physical infrastructure and the concrete applications appear to be far from settled in the eyes of those who generate these practices and in the eyes of scientists. This label covers equally and without distinction common routine practices and those which exist in the form of laboratory protocols, or research projects being mounted. At the same time as a tangible reality, nanobiotechnologies have, since they first emerged, been spontaneously integrated into formalized dialogue and placed under the responsibility of the public authorities, as evidenced for instance by the operation “NanoDialogue» financed by the European Commission. The content of this initiative is akin to the formulation of hopes and concerns following a pedagogical position and “ethical” checking. From the interviews, it is quite clear that the way 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:

“clearly our products do not interact, their mode of action is not based on interactions with living material. So we are far from drugs. And fully in the realm of the medical device.” (as we already underlined previously)

4. **The transfer of European ethical standards to emerging countries.** The development of automatic screening processes was carried out in one of the newly associated 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. Acquiring legitimacy for these companies is related to anticipation of the risks and breaches observed in other countries: *“What happens in England, this extreme situation took place as there was a big scandal because a pathologist was collecting organs from deceased babies [...] And there was a big scandal and this is the backlash 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 “do not worry about that” because we do oversee this ourselves.”*

5. **The role of patient associations in the production of ethical standards.** One of the biotech studied has the legal status of a non-profit association. It appeared in France in 1994, at the same time as the enforcement of the first legal regulations concerning bioethics. It is within this structure that good ethical practices concerning some elements of the human body were extended to various types of biological specimens (DNA, tissue, blood cells, frozen lymphocytes, embryonic stem cells, etc.) and to the associated activities (sequencing, genotyping, cell therapy, research on embryonic stem cells). A first version of a traceability software for these elements was also established. From the outset this association insisted on the responsibility of a professional group facing patients and focused particular attention on drawing up standards for consent: *“We had consent from the outset. When I arrived, I saw... 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.”*

6. Cultural and ethical differences

Several of the people interviewed mentioned ethics as having a cultural basis, which should enable the differences observed in European countries and within the United States to be distinguished. This is particularly illustrated in the field of embryonic stem cells and the debate arising from research concerning these cells.

These cultural differences influence the regulatory authorities as to the means of assessing the dossiers, in particular by insisting on the differences between the Food and Drug Administration and the EMEA. But they can also be observed when ethical bodies are mentioned in order to obtain an opinion: “*Yeah, (it is related) to the cultural and ideological beliefs of that person. And that makes it very difficult because if you talk to a bioethicist in [...] who is more, say, linked to the Catholic university of [...], or you go to somebody from [...] it’s not the same answer you get.*” or again à propos the public debate over embryonic stem cells: “*The Brits and the Scandinavians. There is not a shadow of a doubt about that.*”

Some complementary elements from the qualitative analysis, that were not suitable to be included in the questionnaire

The corpus of texts constituted from the interviews with heads of biotech companies is rich for above all it is about the history of their practices. It gives us a good insight into the manner in which ethical concerns and the company have taken form over time. This longitudinal dimension is difficult to grasp from analysis based on a questionnaire, even if a broad sample of companies is included. Only the information obtained through direct interviews with industrial actors can inform us as to how a tangible culture or a given organization, 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 give indications concerning *path dependency* (Liebowitz & Margolis, 1995) 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 made in the future. This influence of the past is very strong as long as the activity of biobanking in France is concerned, as one interview with the head of a company in France showed. Thus, as they grew, the first biobanks (particularly the first national biobank) 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 regards to the use of the biological samples (to be studied for a given disorder). To this end, the representatives of a patient association were actively present when the regulations concerning bioethics were revised so that the consent to make a donation could be extended to a broader range of research and uses of biological material. The aim was that all material arising

from a donation contained in the biobank might be able to be used for the wider research perspective. Today, the ethical procedures concerning confidentiality, the secondary use of specimen, and of sharing data, tend to come into line independently of the type of biological material in the biobank. The way to produce good ethical practices is in relation with a strong *path dependency* of the initial organizational outline of the biobank. It is also this biobank which was the first to obtain a national authorization to store human embryonic stem cells from the Biomedicine Agency, thanks to the requirements for traceability that it had already established for other biological materials. This *path dependency* also affects for example the practices around “by-products” of embryonic stem cells (such as the precursors of mature cells, i.e. 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 (research, storage and importation of human embryonic stem cells is subject to waivers delivered by the Biomedicine Agency). The actors interviewed would like to see unification of these two regulations and a less constraining regulation covering clinical trials based on cell therapy products. Despite the same therapeutic action and a biological proximity between cell therapy products and differentiated products which are “by-products” of embryonic stem cells, their production, as regards to ethics, is not part of the same history of practices. This is relevant in the manner in which debate about ethics is being shaped and becomes part of the history of technical processes.

Conversely, producing ethical standards also comes into play in the manner in which scientists organize their research as described in the following sentence: *“But what is important is that the patient him/herself has given their consent. For example, for Gaucher’s disease a register was set up and, after treatment, the doctors always 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 large group, and with wider results so that consequences can be drawn to improve clinical practice and the product, if necessary, the manner of treatment, everything in fact.”* The recommendations of good practices prescribed for clinical trials indicate a *path dependency* as regards their widening, offering favourable conditions for the implementation of multicentre protocols.

Originality and discussion of the framework of analysis in relation to existing literature.

The ethical practices combined with industrial activity are intimately intricate with the emerging technologies themselves, that were examined in this study. They correspond to innovative practices, not necessarily in the sense of a recognized performance of the products considered but rather because they are the coherent result (Knorr-Cetina, 1981 and 1999; Pickering, 1995) of a complex “knocking-together” (Ciborra, and Lanzarra, 1994). This “knocking-together” is both

the product of a remarkable technical assembly and an agreement between multiple actors (academics, patient associations, manufacturers) who have got together over a technological project (Latour, 1989; Tournay, 2007). So much so that the project dimension is at the heart of the process of constituting these innovations. This situates our study in line with the works which claim to derive from the sociology of expectation (McMillan, 1979; Nowotny and Felt, 1997; Van Lente and Rip, 1998), which claim a close 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 fears and promises for mankind. Through this theoretical detour, we can see the importance of studying the debate about ethics as an element likely to contribute to the harmonization of technical arrangements. Before being technologically ready and certain in terms of prospects for treatment, all these practices will be subject to some level of regulation by professionals or by public authorities. They place the concerns of society at the heart of their process, many bioethical recommendations often go hand in hand with this regulation when it occurs. The production of ethics then has practical effects in real time on the construction of this future, such as the production of good practice guides and supervision of these new technologies. These practical effects are comparable to *Prospecting Retrospects* (Brown and Michael, 2002), heralding a future in the making, they are the basis for concrete supervision of medical innovation.

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The above text will be the main part of the article to be submitted in 2008 to a social sciences journal.

4.2 QUANTITATIVE SURVEY AND COMPLEMENTARY INTERVIEWS

The following steps were followed:

- Elaboration of the questionnaire
- Iteration of the questionnaire within the steering committee and scientific committee
- Mounting of the questionnaire in an on line tool and testing it for operationality
- Sampling among European biotech companies and sending the information to this sample through the national associations
- Gathering fo the results and analysis
- Presentation of the results and discussion in First Conference
- Complementary interviews, if necessary
- Redaction of the results and synthetic article for a biotechnology journal.

4.2.1 Elaboration of the questionnaire

The above analysis paved the way for the questionnaire conception.

4.2.1.1 From qualitative interviews to the questionnaire

The aim of the qualitative analysis is to discuss in even greater detail the nature and importance of the reflections concerning ethics produced embedded in the emerging technologies, in relation to the country under consideration, and the particular nature of each of the technologies considered. The primary corpus of texts arising from the interviews has been used with the purpose of drawing up a more general questionnaire that was sent to a much wider group of companies⁵ (sixty). 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 grouped into two sets enabling careful analysis and the drawing up of the questionnaire. On the one hand, the analysis explored 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 implementing solutions into concrete practices (1). On the other, hand from the responses given, we then identified the references on which the various means of resolving the bioethical questions were based (2). Conversely, these complementary approaches allow us to check whether the elements obtained during the interviews for each biotech sector were

⁵ 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 scientific and executive committee of this research, including European Academics and European Representatives of Industrial Partners.

representative and were key elements for establishing what stands out as the decisive ethical standards for the sectors of activity studied. Then we could distinguish the more anecdotal elements from those more fundamental and those specific to a given company. One will see here the interest of studying local discussions about ethics which emanate directly from the production sites to draw up a research methodology around these questions which are difficult to grasp. By paying particular attention to each local scene, our bottom-up approach directly addresses 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 (Noble, 1984; Barry, 2001). But there is more. The corpus of texts constituted from the interviews with heads of biotech companies is rich for above all it is about the history of their practices. It gives us a good insight into the manner in which ethical concerns and the company production have taken form over time (3). This dimension is necessary for establishing a co-production model of moral statements and material practices, as Margaret Lock shows for example, between the transformation of transplant practices and the benchmarks of death definitions (Lock, 2002). Thus the questionnaire is constructed not from an exclusively a priori defined set of concepts but, on the basis of considerations about ethics actually expressed by actors of the field. This is meant to address their views and concerns and not those pre-defined by the investigators involved in the project or any institutionalized or pre-constructed views about bioethics.

4.2.1.2 Iteration of the questionnaire within the steering committee and scientific committee

Several versions of the questionnaire were produced. The first version was done by the two persons who had performed the interviews and the qualitative analysis. Then it was reviewed by the head of the scientific committee, then by the coordinator.

This resulted in a second version that was circulated to the executive committee, followed by a telephone conference and further modifications were made.

It was then circulated to the entire scientific committee and presented and discussed at a specific meeting of the scientific committee (July 2007).

After extensive discussion, it was modified, restructured with three general orientations:

- a) to incorporate not only elements from the interviews but also elements that appeared as key points to members of the scientific committee
- b) to make it easier to fill in
- c) to make it shorter.

The way it would be administrated (postal format, e-mail attachment or in an on line tool was also discussed and the decision was taken to opt for an on line tool after further validation and with possibility to download it and prepare “off line” the various answers, potentially involving several persons in the company.

Then it was again circulated to the executive committee members and tested.

- The final document is in appendix 3; it comprises a total of 153 questions distributed over 3 parts,
- One general, this first part was dedicated to the general approach of Bioethics in the company, common to all respondents.(24 questions)
- A second part depends on the field of activity covered by the company
 - Bank of human biological samples (Questions 25 to 50: 26 questions)
 - Cell or Gene Therapy (Questions 51 to 68: 18 questions)
 - Stem cell R&D (Questions 69 à 93 : 25 questions)
 - Diagnostics and related tests (Questions 94 to 104: 11 questions)
 - Nanobiotechnology (Questions 105 to 121: 17 questions)
 - Clinical trials (Questions 122 to 137: 16 questions)
 - Others: (Questions 138 to 147: 10 questions)
- A third part: open questions and free contributions. .Questions 148 to 153: 6 open questions + free commentaries possible.

4.2.1.3 Mounting of the questionnaire in an on line tool and testing it for operationality

After testing and validation of the questionnaire by the executive committee, France biotech was in charge of mounting it in the online tool where it was then tested by members of the scientific committee to verify the functionalities. The questionnaire was downloadable in order to allow preparing the answer if more than one person or one time slot had to be involved. The tool chosen was “Survey monkey” as it is allowing a clear questionnaire layout online and it enables to skip easily the questions which are not relevant for a respondent. Consequently, depending on the fields of activity of the company, the questionnaire would take more or less time. This tool also allows a satisfactory aggregation of answers while allowing also a .pdf version of each individual anonymized answer. It can be accessed at the following URL: http://www.surveymonkey.com/s.aspx?sm=LWGrUgbgU1DvjJSdW1BLRg_3d_3d

4.2.1.4 Construction of the sample among European biotech companies, methodology and sending the information to this sample through the national associations

The sample has been constructed in order to be representative of the various scientific orientations of the biotech companies in the various countries and the questionnaire sent to 10 to 15 of them. If less than 15 companies for a given orientation were registered in a given country, the questionnaire would be addressed to all of them. For the selection of the enterprises see appendix 4. Sixty-eight companies were solicited for filling in the questionnaire over 9 countries (Sweden France, Hungary, Spain, Estonia, Germany, Canada, Belgium, UK).

Anonymity of the answers was offered as an option (but the fact that a company has answered will be separately kept as an information for survey completion). A second call for answers was directed to the non responders by E-Mail, with the requirement of a contact person specifically for this study. After two further weeks, if no answer had been obtained one telephone solicitation was done.

The role of national associations was extremely important both for the choice of companies and the help to get answers.

A statistical analysis was performed on answers to closed questions. A common grid will be designed for analysis; some additional variables were constructed from the answers; main results are to be exploited as a typology of themes and their way of being addressed, in order to inform the design and content of the observatory.

A supplementary analytical survey was envisaged on "open-space" questions if they had been felt leading to new developments which were not anticipated. The answers to these open questions were analysed in two ways: 1) to construct a detailed list of themes and preoccupations expressed by professionals from industry; 2) for those accepting it a specific semi-structured interview done by a sociologist would be directed to a number of companies mentioning questions or views considered by the scientific Committee as important to deeply investigate. A maximum of 30 such interviews would be conducted (in English or in the language of the country according to the cases), recorded if allowed. However this step was not considered as necessary after the questionnaire survey and it was felt that conferences discussions would be sufficiently informative. Reactions through the use of the observatory and forum and frequently asked questions are expected to provide more information than a new round of questionnaire or solicited interviews. However the scientific committee suggested that the questionnaire could be also addressed to large companies as a comparison and this will be done in a complementary work after the production of this deliverable in order to inform the discussion part of an article.

A cross analysis by domains and by countries has been done and is summarized below. The results of the statistical analysis and analytical survey will be disseminated throughout the consortium. After validation by the Scientific Advisory Board, the final report will be confronted with the data coming from the Conferences.

4.2.1.5 Gathering results and analysis

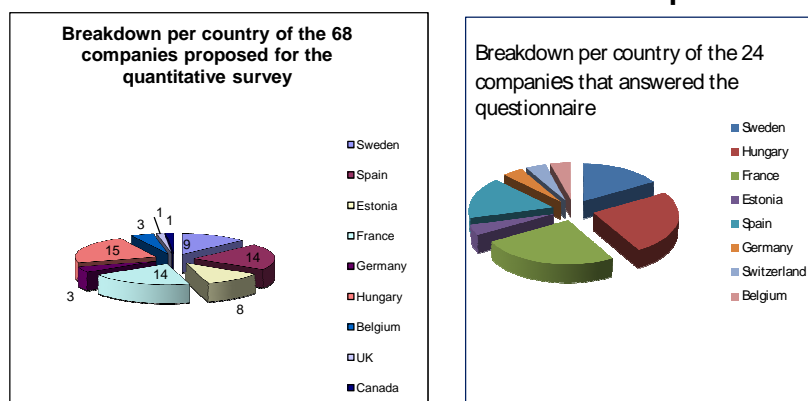
Questions in the questionnaire for the quantitative analysis were grouped in three different parts:

- Questions addressing the general approach of bioethics within the company
- Sector-specific questions
- Open questions for identifying emerging issues.

4.2.1.5.1 Respondents:

The questionnaire was prepared on-line and sent over to 68 biotechnology companies in nine countries ((Sweden France, Hungary, Spain, Estonia, Germany, Canada, Belgium, UK). Twenty four replies were collected (35%), 13 were fully exploitable. For 10 others only the general part (part 1) was documented. This level of answers limited the statistical analyses but at the conference it was considered as informative and useful for the next steps as this is a unique set of information. However the discussion on the feasibility of a long questionnaire in a context of time pressure in the companies that had been a concern of the scientific committee revealed to be an obstacle. The preoccupations of the companies are probably better targeted at the occasion of questions in front of a given practical situation.

Companies targeted in 9 countries (N=68) Answers from 24 biotech companies



13 answers fully exploitable, 10 on part one only, 1 too incomplete

4.2.1.5.2 1st part of *the* questionnaire (General questions).

The answers are described below.

Who answered the survey ?

52% of the respondents were founders of the company

37% of the respondents were Chief Executive Officer (CEO) of the company

17% of the respondents were Chief Scientific Officer (CSO) of the company

20% of the respondents were either Chief Medical Officer (CMO)(3%), or Regulatory affairs and Legal executives (7% and 10%)

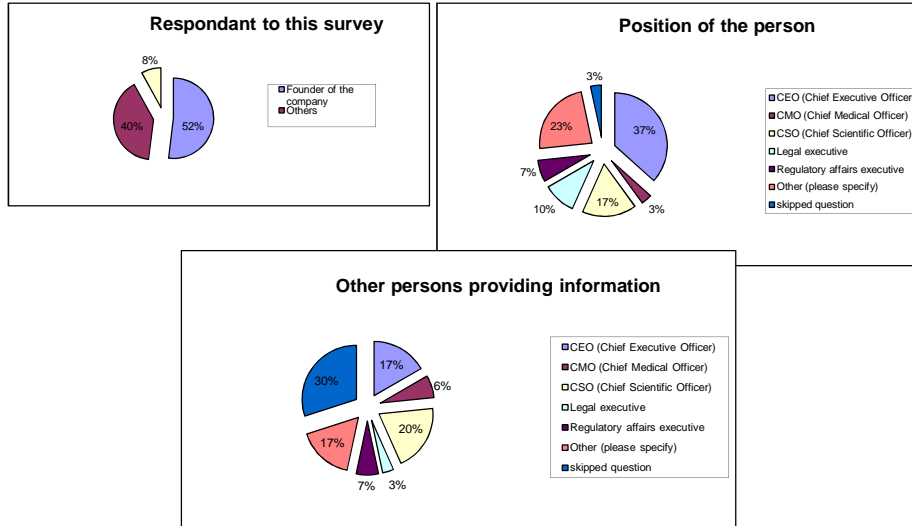
23% of the respondents occupied another position, non specified

Among other persons providing information for the survey:

20% were CSOs

17% were CEOs

The respondents



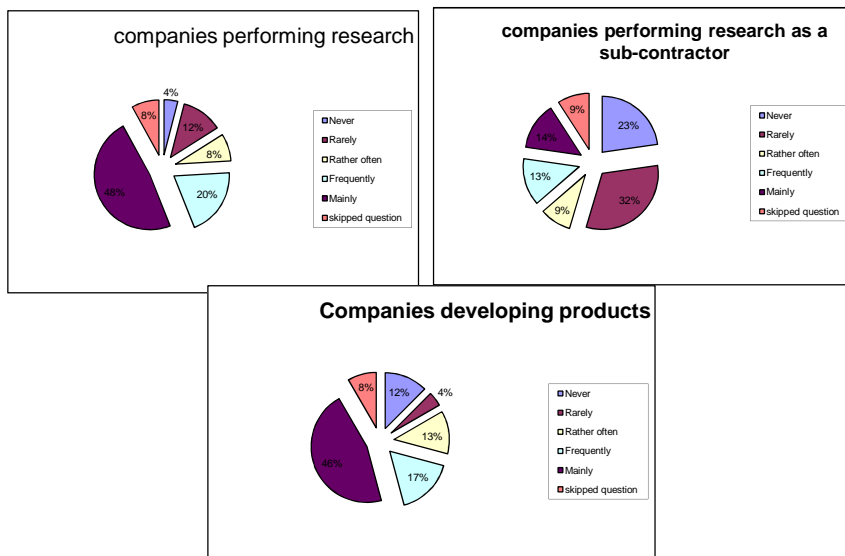
Activity of the company

48% are performing research

32% rarely perform research as a sub-contractor or in partnership with other industrial corporations

46% are developing products

Activities of the companies



Participation in ethics-related activities

12% have employees that are members of external ethics committees

16% of the companies have an internal ethics committee

60% do not have an internal ethics committee

Tools of reference for ethical issues

12% refer to an internal ethics committee

12% refer to a chart of ethics

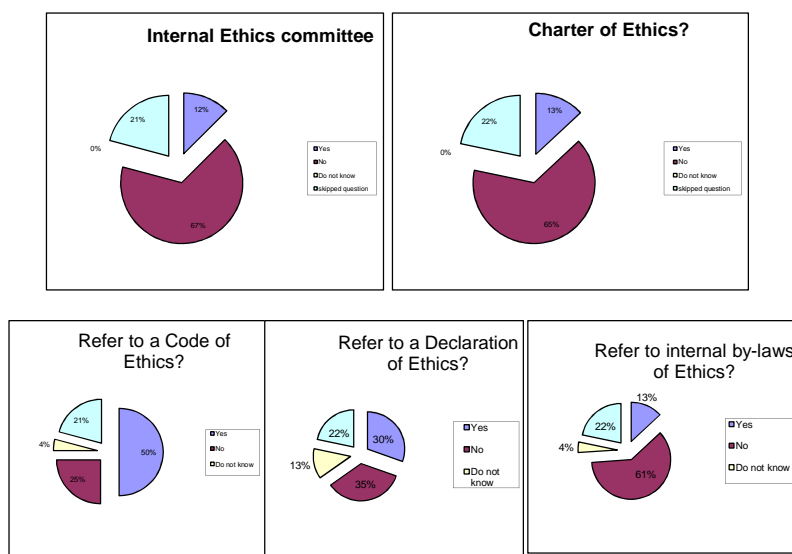
50% refer to a code of ethics

30% refer to a declaration of ethics

13% refer to internal by-laws of ethics

This question reveals the strong desire of the industry to refer to a regulatory framework .

Reference for ethics



Companies generally go for external advice at the national level.

36% of the companies seek external ethical advice

45% go to the National Ethics Committee for advice

7% go to the European Committee of Ethics

No one declared looking at an International Committee of Bioethics for advice

Bioethics issues are broadly taken into consideration in the companies research, development and marketing strategy ; bioethics issues interfere less in the company strategy for raising money, in the intellectual property issues and for preparing corporate promotion.

- 70% of the companies surveyed consider bioethics issues as a parameter in strategic choices in R&D

- 67% of the companies take bioethics issues into consideration when preparing their business plan

- 47% of the companies take bioethics issues into consideration when raising money, 41% never or rarely take them into consideration

- 76% of the companies take bioethics issues into consideration when developing partnerships

- 47% of the companies consider bioethics issues in intellectual property strategy

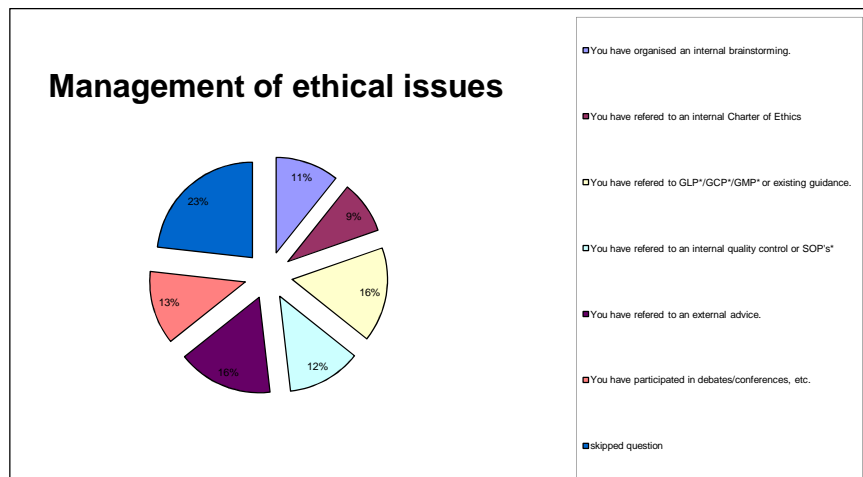
- 47% of the companies take bioethics issues into consideration in corporate promotion

- 76% of the companies take bioethics into consideration in product development and marketing

When questioned about the most applicable bioethical principles applicable to their activities, companies mentioned by order of relevance:

- Informed consent (100% of the responses)
- Benefit/risk analysis (87,5%)
- Animal rights (84,62%)
- Integrity of human being and non discrimination (78,57% to both questions)
- Precautionary principle (71,43%)
- Dignity of human being (64,29%)
- Autonomy of the person (61,54%)
- “Commodification” of the human body (41,67%)
- Reification of the human person (30,77%)

How companies deal with ethical issues



When companies are facing ethical issues, they generally manage them as follows:

- Referring to an external advice (83,33%)
- Referring to GLP*/GCP*/GMP* or existing guidance (76,92%)
- Referring to an internal quality control or SOP's* (66,67%)
- Organising an internal brainstorming (63,64%)
- Participating in debates/conferences, etc. (58,33%)
- Referring to an internal Charter of Ethics (45,45%)

GLP* = Good Laboratory Practices

GCP* = Good Clinical Practices

GMP* = Good Manufacturing Practices

Bioethical issues have impacted the daily practice of the companies as follows:

- Adopting SOP's or a Quality Control System
- Introducing more patient data protection
- Introducing new communication procedures
- Introducing new procedures for disclosing R&D results and increasing internal training

Individual information of persons and consent procedures are a source of concern for 64% of the respondents ; they are relevant but externalized in 45% of the companies respondent.

When asked about their understanding of the meaning of “informed consent”, the responses by the companies found the following “fully relevant”:

- It is a legal obligation (80%)
- It allows individuals expressing their autonomy (73,33%)
- It protects individuals dignity (64,29%)
- It is an instrument of dialogue (35,71%)
- It is a way of formalizing a contract (20%)

The majority of respondents (56,3%) found that bioethical issues in the company were related to identifiable risks, identified as follows by order of importance:

- Informational risks in breach of confidentiality (85,71%)
- Physical risks for patients and difficulties in delivering the accurate information about the risk to the participants (75% to both items)
- Difficulties in delivering the accurate information about the risk to patient groups and difficulties to assess the information understanding about the risk by patient groups (62,50% to both items)
- Difficulties to assess the information understanding about the risk by the media (55,56%)
- Difficulties in delivering the accurate information about the risk to the media (50%)
- Difficulties in delivering the accurate information about the risk to society and difficulties to assess the information understanding about the risk by society (44,44% to both items)
- Environmental risks: hygiene and security (37,50%)
- Physical risks for personnel involved (28,57%)
- Informational risks in discrimination (14,29%)

There was no striking differences between countries in the answers; it thus seem feasible to consider information at EU level.

As a conclusion of this first and general part of the questionnaire, one can say that this limited set of data is rich of information; it allows to underline several characteristics of ethics as seen and managed in the companies:

- Ethics is seen by the companies in terms of laws and regulations, and ethical concerns are embedded in the company practice and intricated with technical and quality aspects
- “Classical” medical ethics is present in particular in the context of clinical trials
- There is a strong desire among the industry to be able to refer to a regulatory framework
- The European regulatory level is seen as relevant, if harmonized all over the EU member states.

4.2.1.5.3 2nd part of the questionnaire: domain specific aspects:

No proper statistical analysis was done given the low number of responses, but the main information is summarized below:

Biobank

Seven companies had a biobank and for 4 of them it was of a size between 100 and 1000 sampled individuals. Biological samples stored were blood and blood components in 4 cases and DNA and nucleic acids, cells and cell lines in 3 cases. Multiple products stored was a general practice, and they were freshly obtained in the majority of cases. The purposes were for scientific studies and therapeutic applications, but no company mentioned genetic studies.

A formal procedure had to be applied, with at minimum a consent which appeared to be variable in scope (for storage, for use, for transfer, for data processing). This activity was regulated through a national legal framework in 6 cases and a European legal framework referred to in 5 cases. The relevant level of regulation was described as European in all 7 cases. In 5 cases the existing framework was considered rather well or fully adapted. However 4 respondents expressed the view that a new legal framework was needed for biobanking, but the level for this framework was differently considered by those respondents (national European or international were all cited). Medical and identifying information are usually stored. In one third of the cases they are anonymized. Personal information is usually not transferred and the internal use of samples and information is the major use. An interesting point was that the role of material transfer agreements as regards to ethics was very differently considered from no role to a management tool for such issues. This can be regarded as a suitable domain to implement ethics.

Gene or cell therapy

Seven companies were having such activity but only 3 mentioned ethical issues related to it. In only one case was this considered as a frequent event and in 3 cases at a specific step of the process only. Conversely, this activity was regulated by a legal framework in all 7 cases, at European level in all cases and most of the time at national level also. But the level of relevance/adaptation of the framework was differently appreciated from poorly adapted in 3 cases to fully adapted in 3 others; 4 respondents considered that a new legal framework was needed, at international level. This might be related to the fact that in 4 cases the regulatory category of the sample/product was reported to be a source of important concern. Some kinds of specific recommendations or good practices guidelines were used in all cases. The ethical aspects mentioned did not relate to patenting or commercialization.

Stem cell research

Six companies were practicing stem cell research and development activities, all of them at least with human stem cells, but none of them with embryonic human stem cells. No specific ethical issues were reported, and a legal framework, at least at national level was applicable to the activity, fully implemented and considered as well adapted. However 2 respondents considered that bioethical issues in stem cell use required the implementation of a new specific legal framework, at international level. All respondents are using specific recommendations or good practices guidelines.

Diagnostic tests

Only 5 companies reported to develop an activity in diagnostics or related tests. They were pharmacogenetic or biomolecular tests (biomarkers). Bioethical issues were reported in relation with test assessment, patentability, information to patients and choice of the target population. Thus all these aspects might well be of relevance for the observatory. In only 3 cases a legal framework was implemented for this activity and was considered well adapted. Only one respondent felt a new specific legal framework was needed. All respondents are using specific

recommendations or good practices guidelines and are aware of the existence of other such documents.

Nanobiotechnology

Five companies reported activity in this domain. Ethical issues were reported regarding clinical application, technology assessment and commercialization. In 2 cases it was felt that there was a link between the degree of advancement of the production and the formal occurrence of bioethical questioning. Also the product's specific mode of action raised bioethical issues in 3 cases. This was related to risks linked to the introduction of particles. No legal framework was applicable as mentioned by 3 respondents and 2 of them considered that it would be necessary to get one. Respondents mentioned less than in the other domains the use of specific recommendations or good practices guidelines and are not aware of the existence of such documents. There is certainly here room for dissemination of European texts and documents in this domain that have been relatively recently produced.

Clinical trials

This activity was reported by 5 companies, mainly in drug testing, in various clinical contexts, 3 times cancer, but in many other kinds of pathologies too. Ethical concerns are reported for the design of the protocol, the choice of the target population (adults in most cases, children in one, case). Procedures have been established for disclosing results of clinical trials for medical peers in priority, but also for business options and patients, The legal European framework related to clinical trials was referred to in all cases, was reported as fully implemented and rather well adapted to the activity in 3 cases whereas it was considered poorly adapted in 2 cases. However a new legal framework was only considered necessary by one respondent, at European or international level. The body companies refer to for the protocols' ethical approval is always a local research ethics committee and sometimes in addition a national ethics committee. Specific recommendations or good practices guidelines are always used mainly of European level. Whereas in most cases the authorisation procedure established by the clinical trial EU directives is considered by the companies as correctly implemented in their country, one report a poor implementation ; Three companies find poorly adapted the mechanism in place for the protocols' ethical approval.

Two companies only mentioned developing an activity which was different from Biobanking, Gene or Cell therapy, Stem cell R&D, Diagnostics or Nanobiotechnology (tissue engineering, drug development system in general, which implied clinical trials). This shows that the domains targeted were covering the main activities of the companies who answered.

As a main conclusion on the specific domains one can underline that recommendations, guidelines and good practices are widely used when they exist, that companies do not engage in aspects that raise the strongest ethical issues and that regulation at international level, that facilitates international level activity is a strong demand.

4.2.1.5.4 Third part of the questionnaire: open questions

Very few companies did take the time to give more information; the questions were related to bioethics definition, bioethics as an obstacle or not in company activity, aspects of qualification

of products, externalization and issues created by international dimension, for example in clinical trials.

To the question “**Do you see bioethical questions as a serious obstacle to your activity; or as providing interesting opportunities? Give examples or details.**”, two companies provided detailed input as below while 6 answered simply “no”.

Company 6:

“Most of the bioethical questions came from clinical trial activity. It seems clear that the increase of regulatory demand could become an obstacle. Clear differentiation of POC (proof of concept)/FIM (first in man) studies and long term clinical development in the guideline and regulatory practice could be a great help.”

Company 9 :

“Bioethical questions are relevant and should be addressed in a non-political manner. The discussions related to the ATMP-regulation in the European Parliament were in part overloaded by Ethical concerns. It would be of great help, if ethical questions could be discussed separately from implementation of more technical regulations or guidelines. As long as each MS has the right to set up own ethical regulations these questions should not delay regulations which are set up to provide EU-wide harmonization of marketing authorisation procedures. With respect to the activities of our company it is welcomed that there are increasing activities to include patient groups into the decision making process.”

Company 20

“Since the endusers of our products are people who are concerned by bioethical questions it is wise to incorporate these issues in the R&D and business plans as early as possible.”

These 3 remarks express different concerns, one of the need of definition and clarification of trials that do not fit with the classical phase 1 to 4 classification, the second is asking for a better separation of topics being ethics related or not and the third is expressing a very general pragmatic and market oriented attitude considering the consequences of ethical preoccupations among the end users, but not implying any positioning on ethical aspects themselves by the company. These views will have to be conveyed to relevant authorities, and they are impregnated of pragmatism; the observatory could include a forum where people could ask questions or make remarks of that type in order to construct a list of issues and elements that could then be considered by relevant authorities or committees.

To the question: “**Is the European scale, or the broader international scale, raising different bioethical issues or difficulties as compared to your national situation? Can you give examples?**” Company 20 reported that “Countries where regulations are not implemented can attract hopeless patients who are desperate to get any experimental treatment.”

It was striking to see that the question was taken from the point of view of patients and not from that of a company, regarding regulations more or less stringent. This evoking a sort of “clinical trial tourism” but is not substantiated by examples.

To the question:” **Are there activities you would foresee externalizing/relocating because of regulatory aspects?**”, two companies answered:

Company 16: “Cryo preservation of samples for family use”, with no specific comments on why this should be done; it can be considered that a long term potential use by family members could not be seen as being the responsibility of the company.

Company 20: “No. We choose to lobby for reasonable local regulations.”

This is also a very pragmatic answer and allow to underline the fact that companies are eager to have their own voice heard, also in the regulatory domain regarding bioethics, as is the aim of this project.

On the qualification of products oen company recalled “There was a very heated legal debate on cord blood banks, if it is a "clinical trial".”, which als show that companies follow the debates that can impact on their field of cativity quite actively.

The question: “**Are there bioethical issues of relevance to your company that, to your knowledge, have not been addressed appropriately by a relevant ethics committee? Give examples.**” raised the following answer by Company 9:

“The coming technical guidelines for ATMP (Advanced Therapy Medicinal Products) will most likely require preclinical trials in animals also for already marketed products. This should be avoided.

In addition, it is of concern that the different national health systems inhibit the access to innovative technologies within Europe despite the fact that a Market Authorization has been achieved due to different and additional requirements for reimbursement. Therefore, from our point of view the questions arises, why harmonising marketing authorisation procedures by not addressing the accessibility of these "harmonized" products within the EU as well?

In addition, it is still under discussion how much money may be spent for the treatment of chronic diseases per patient. Finally in our case it is also a matter of bioethics when an "old" technology, however, included in the DRG (Diagnosis Related Groups) system, is reimbursed much more easily and better than a new technology with clear cut benefits for the patients with respect to quality of life, which is not part of the DRG system and even worse, which induces LESS costs.”

This comment is of interest as it shows the inclusion of justice and economical issues in the ethics arena, and as it challenges the administrative slow process of changing systems in terms of ethics.

The questions on ethics and bioethics definitions did not raise any specific reactions except for one company who remarked that “Bioethics is a part of the Ethics”.

All these results were presented and discussed at the First “GMP to GBP” Conference organized in Brussels the 4th of December 2007 (see corresponding report Conference as project deliverable). They raise major interest but complementary interviews were not foreseen as necessary, because the qualitative interviews had already given a lot of information.

Rather the issues addressed will be embedded in the observatory and the documentation made available will take the results into account; the web platform should also incorporate a possibility of forum of questions as companies obviously are more motivated to address a question that preoccupies them at a given time rather than filling in questionnaires.

Redaction of the results has been done after the Conference and synthetic article is envisaged for a biotechnology journal, after the next meeting of the scientific committee, who will be consulted about a suitable journal.

5 Conclusion

- As a general conclusion, the survey on ethical practices in biotechnology companies used a set of methodologies from choosing domains of activities, companies, qualitative interviews and extensive questionnaire. This set of elements that required a very good cooperation between all partners provided a clear picture of the following situation:
Qualitative and questionnaire data are in agreement, showing that
 - ethics is mostly viewed in terms of legal requirements, but that professional and national/international regulations are also used
 - the European regulatory level is seen as a relevant level of regulation
 - there is a frequent demand of new regulatory framework
 - there is a demand for clear cut regulation that do not mix up technical and ethical requirements
- Companies are eager to have their voice heard and show interest in the issues, as well as a pragmatic approach of ethical aspects
- The timing in setting up regulations for new biotechnology based products is perceived as slow
- The utility of the observatory that is envisaged is now informed by this survey.

6

APPENDIX

Appendix 1 – Qualitative survey – List of companies / Face-to-face interviews: breakdown by country and topics

From GMP to GBP Qualitative survey, companies involved: breakdown by country and topics (as of 15/06/07)

| | 2: Stem cell research | 2: Gene & Cell therapy | 3: Nanobiotech | 4: Biobank | 5: Diagnostics | <i>Number of companies per country</i> |
|--------------|-----------------------|------------------------|----------------|------------|----------------|--|
| France | √ | | √, √ | √ | | 4 |
| Sweden | √ | | | | | 1 |
| Spain | | √ | | √ | | 2 |
| Hungary | | | | | √ | 1 |
| Belgium | √ | √ | | | | 2 |
| TOTAL | 3 | 2 | 2 | 2 | 1 | 10 |

Appendix 2 – Qualitative survey – Interview Guide

1. History of professional trajectories and organisational characteristics of companies

- Number of actors and professional trajectories
- Current activities
- Training and specialties field
- Organisational features (closely ties to some other organizations : ethics committee or regulatory agencies, national or international activities, bureaucratic or liberal forms of organization)
- Presence of or relation with patient groups
- Collective strategy in the long run
- Bioethics concerns prior to working within the company

2. Characteristics of technical processes setting within companies

- Innovating grade of the process (closely related to regular medical practices or experimental device; working routines in the making : beginning and shaping)
- Procedures including human body elements conservation
- Function of traceability procedures
- Management of risks related to the innovating process
- Process for patient consent if appropriate (solved or not)
- Pipe-Line products
- Patents filed
- Difficulties to be overcome (technical, economics, marketing)
- Ways of disclosure of information; to whom?
- Future prospects of the company

3. Conditions of bioethical issues within companies

- Moment when bioethical issues appear in the history of the company, if they appear
- Actors of these issues (internal, external, media, pressure, closely ties to the company or completely external)
- Internal or External process of bioethical concerns
- Personal approach or related to strategy or claims (in order to legally protect company activities, to allow developing company activities on a large scale with different human elements)
- Correlations of the importance of bioethical issues with the innovating grade of the process

4. Pragmatic features of bioethical issues within companies

- Existence of managing principles or statements (precaution, dignity, donation etc.) of actor's actions.
- Leading informal rules (management of risks)
- Constitution of internal committees
- Constitution of practice guidelines
- Emerging issues in new European countries
- Mediatization of bioethical issues

5. Elaboration of standards of practice guidelines

- Key-actors (closely tied with bioethical stakeholders?)
- Context of appearance of practice guidelines (legal applications or/and internal elaboration)
- Conditions of establishment of working routines with other groups (patient, committee ...)

Current stakes and future prospects concerning standardization

SIXTH FRAMEWORK PROGRAMME
PRIORITY: Structuring the European Research Area
SCIENCE AND SOCIETY



Contract for:

SPECIFIC TARGETED RESEARCH PROJECT (STREP)

Questionnaire for quantitative survey – WP2

Project acronym: **From GMP⁶ to GBP**

Project full title: **From GMP to GBP : Fostering Good Bioethical Practices (GBP) among European Biotechnology Industry**

Proposal/Contract No.: 036806

Date of preparation of the questionnaire for the quantitative survey- WP2: October 2007

Start date of contract: *October 2006*

NB : after validation the questionnaire below was slightly modified in its lay out and was mounted in an online tool accessible at:

http://www.surveymonkey.com/s.aspx?sm=LWGrUgbgU1DvjJSdW1BLRg_3d_3d

⁶ Good Manufacturing Practices

Questionnaire about bioethics practices in the European Biotechnology Industry

As a European Biotechnology SME's, this questionnaire is built to help to raise the bioethical issues you are confronted with every day. Thanks to this European project, the SME's all over Europe will have the opportunity to bring the SME's voice in the European Bioethics debate.

This questionnaire is divided in three parts:

-The first part is dedicated to the general approach of Bioethics in your company and is common to all respondents.

-The second part depends on the field of activity covered by your company; you will be oriented to different sub-sets of sector-specific questions.

- The third part gives you opportunity to add own views if you so wish.

Therefore filling in the questionnaire will take you from 15 to 30 minutes, depending on the scope of activities covered.

The identification of respondents requested below will be used only for the data collection process and for evaluating the representativity of the sample of responding companies.

Data collected in the second part will be anonymised, encoded and published in an aggregated form to ensure confidentiality.

A. Identification of the respondent:

- 1) Company name:
- 2) Address:
- 3) Name of the person with overall responsibility for the questionnaire:
- 4) Position of the person with overall responsibility for filling in the questionnaire:
- 5) E-mail address:
- 6) Telephone number:

Company Code:

(to be filled in by the Questionnaire Manager of the GMP to GBP project)

B. 1st part: General approach of bioethics issues in your company

1. Is the person with overall responsibility for responding to this survey a founder of the company ?

YES NO

2. Position of the person responsible for responding to this survey:

- CEO (Chief Executive Officer)
- CMO (Chief Medical Officer)
- CSO (Chief Scientific Officer)
- Legal executive
- Regulatory affairs executive
- Other (please specify):

3. Other persons consulted for providing information for responding to this survey
(Tick the right answer(s); tick as many answers as necessary)

- CEO
- CMO
- CSO
- Legal executive
- Regulatory executive
- Other (please specify):

4. Activity of your company

(Please indicate a ranking from 1 to 5 depending on the time and resources allocated to each type of activity; 1=the less important / 5= the most important)

- | | |
|-------------------------------------|--------------------------|
| Research | <input type="checkbox"/> |
| Research sub-contractor | <input type="checkbox"/> |
| Development | <input type="checkbox"/> |
| Services provider | <input type="checkbox"/> |
| Manufacturing | <input type="checkbox"/> |
| Sub-contracting manufacturing | <input type="checkbox"/> |
| Sponsoring clinical trials | <input type="checkbox"/> |
| Sub-contracting clinical trials | <input type="checkbox"/> |
| Conducting clinical trials as a CRO | <input type="checkbox"/> |
| Using animals in the R&D process | <input type="checkbox"/> |
| Other (please specify): | <input type="checkbox"/> |

5. Is any employee of your company a member of an external ethics committee?

YES NO Do not know Cannot reply

6. Has your company established an internal ethics committee?

YES NO Do not know Not applicable

7. Does your company:

Have a Charter of Ethics? YES NO Do not know

Refer to a Code of Ethics? YES NO Do not know

Refer to a Declaration of Ethics? YES NO Do not know

Refer to internal by-laws of Ethics? YES NO Do not know

8. Have you had to seek for an external ethical advice?

YES NO Do not know Not applicable

If yes, please describe the situation:

9. In practice, has your company used or referred to opinions provided by a national, a European or an international Bioethics Committee?

YES NO Do not know Not applicable

If yes, please describe the case:

10. In your company, are bioethical issues a parameter considered in :

| | Never | Rarely | Rather often | Frequently | Always |
|-----------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Strategic choices in R&D | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| The business plan | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Raising money | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Developing partnerships | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Intellectual property | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Corporate promotion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Product development and marketing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Other (please specify) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

11. Among the following notions often referred to in bioethics, which are those that could be the most applicable to or in relation with your activity?

Never Rarely Rather Frequently Always

often

| | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Precautionary principle | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Benefit/risks analysis | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Integrity of the human being | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Dignity of the human being | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Autonomy of the person | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| “Commodification of the human body | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <i>(Definition: When an abstraction is treated as if it represented a concrete, real event or physical entity. In other words, it is the error of treating as a "real thing" something which is not one.)</i> | | | | | |
| Non discrimination | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Precautionary principles | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Animal rights | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Other (please specify) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

12. Have you been faced concretely to one or several ethical issue(s) in your business?

YES NO Do not know

If YES

12a. In practice, how have you managed these ethical issues?

Never Rarely Rather Frequently Always

| | | often | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Internal brainstorming | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Referring to an internal charter of Ethics | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Referring to GLP/GCP/GMP or existing guidance <i>(GLP: Good Laboratory Practices, GCP: Good Clinical Practices, GMP: Good Manufacturing Practices)</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Referring to an internal quality control or SOPs <i>(SOP: standard operating procedures)</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Referring to an external advice | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Participating in debates/conferences, etc. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Other (please specify) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

12b. How have these ethical issues impacted your daily practices?

Adoption of Standard Operating Procedures or a Quality Control system:

YES NO Do not know

New procedures for disclosing R&D results:

YES NO Do not know

More patient data protection

YES NO Do not know

Increased internal training

YES NO Do not know

New communication procedures

YES NO Do not know

If YES, characterize the communication level involved:

Patients-medical doctor

YES NO Do not know

- | | | | |
|--------------------------|------------------------------|-----------------------------|--------------------------------------|
| Colleagues/collaborators | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| External communications | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| With Ethics Committees | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| Other (please specify) | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |

You can specify here the situation(s) encountered if you so wish:

13. Are the individual information of persons and consent procedures:

- | | | | |
|--|------------------------------|-----------------------------|--------------------------------------|
| Practiced in your company | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| A source of concern | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| Relevant but externalized | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |
| Not relevant for your company activity | YES <input type="checkbox"/> | NO <input type="checkbox"/> | Do not know <input type="checkbox"/> |

14. What is your view of the meaning of “informed consent”?

(Please indicate a ranking from 1 to 6 depending on the relevance of the reply; no ex-aequo)

- | | |
|---|--------------------------|
| It allows individuals expressing their autonomy | <input type="checkbox"/> |
| It protects individual dignity | <input type="checkbox"/> |
| It is a way of formalizing a contract | <input type="checkbox"/> |
| It is a legal obligation | <input type="checkbox"/> |
| It is an instrument of dialogue/communication | <input type="checkbox"/> |
| Other (please specify) | <input type="checkbox"/> |

15. Are bioethical issues in your company activity related to identifiable risks/difficulties?

- YES NO Do not know

If YES, these risks concern

- Physical risks €
 - For patients €
 - For personnel involved €
- Environmental risks €
- Informational risks €
 - Breach of confidentiality €
 - Discrimination €
- Difficulties in delivering accurate information
 - to the participants €
 - to patient groups €
 - to the media €
 - to society €
 - to others (please specify) €
- Difficulties in assessing information understanding
 - by the participants €
 - by patient groups €
 - by the media €
 - by society €
 - by others (please specify) €
- Other (please specify) €

16. If risks possibly caused by your activity were not properly assessed and acknowledged, and consequently raise ethical issues, how would you qualify this situation?

- Irrelevant for your company €
- Difficult to manage €
- Requiring external advice €
- Raising debate within the company €
- Problematic for the company reputation €
- Other (please specify) €

17. Do you easily find the relevant information/advice for managing bioethics issues?

National laws and regulations YES NO Do not know

European Directives and regulations YES NO Do not know

International Guidelines YES NO Do not know

External expert advice YES NO Do not know

18. What would help you to manage the ethical dimension of your activity?

- Easy access to regulatory instruments YES NO Do not know
- Tutorials on how to apply them YES NO Do not know
- Participation in debates/seminars YES NO Do not know
- Specialized training YES NO Do not know
- Easy access to expert advice YES NO Do not know
- Other (please specify) YES NO Do not know

19. The kind of information you need should be:

- Regularly pushed on your e-mails YES NO Do not know
- Available On-demand YES NO Do not know

20. Are hygiene and safety of personal a source of ethical concerns in your company?

- YES NO Do not know
-

C. 2nd part – Sector-specific bioethics questions

You are now entering the second part of the survey. This section is dedicated to bioethics questions that are related to specific activities currently being conducted in your company. You may consequently have to reply to some of the questions several times. We would very much appreciate your help in responding as completely and accurately as possible.

1. Has your company established a bank of human biological samples?

YES NO Do not know

1.1. Year of creation of your biological bank (4 digits): _____

1.2. Approximate number of samples from different individuals (please give an idea of the size of the Biobanking activity)

- Less than 100
- 101 – 1000
- 1001 – 10 000
- More than 10 000
- Do not know

1.3. Nature of the products stored:

- Extracted DNA and /or nucleic acids
- Tissues, tumors
- Blood, Blood components (blood cells, sera etc.)
- Organs
- Cell lines
- Cells
- Biopsies
- Other body fluid (urine etc.)
- Other (please specify) : _____

1.4. Donor protection issues:

a Do you have to comply with a formal procedure to collect data associated to the samples?

YES NO Do not know

If yes which one (for example, declaration to an authority and which one, signing a form, get an authorization...)

b. Do you use informed consent within your company?

- for sample storage
- for banking
- for data processing
- for other situations (please specify)

1.5. Purposes and Origin of the samples:

1.6. Purposes of the collection

For Scientific purpose only

For genetic studies

Scientific purpose associated to diagnostics or to other non therapeutic medical activity

Scientific purpose associated to therapeutics

Other (please specify)

1.7. Storage

a) Freshly obtained biological samples YES NO Do not know

b) Already cryopreserved biological samples YES NO Do not know

o Of locally obtained biological materials within the company

o Of externally obtained biological materials

o From local collaboration (same country)

o From international collaboration

▪ Within European Union

▪ Outside European Union

1.8.Uses

For an internal use within the company YES NO Do not know

For transfer to other organization(s) YES NO Do not know

For storage YES NO Do not know

1.9. Type of personal data associated to the samples:

Directly identifying personal data (like name and/or social security number and/or address and/or birth date and place)

YES NO Do not know

Other personal data non directly identifying (profession and/or different place of living and/or place of work)

YES NO Do not know

Genetic data YES NO Do not know

Other medical information YES NO Do not know

Family data YES NO Do not know

Other sensitive data (ethnic origin, religious tradition etc)

YES NO Do not know

Other (please specify) YES NO Do not know

1.10. How do you process personal data associated with samples?

Completely nominative donor data

Donor data encoded

Anonymised donor data

(Anonymised means that you cannot go back to the donor but decoding remains possible, in case of necessity, by other operators)

Completely anonymised donor data

(Completely anonymised means that it is impossible to go back to patient identity for anybody)

Others(please specify)

1.11. Biological samples and associated personal data transfer procedures

a-Are there plans concerning data transfer for original personal data?

YES NO Do not know

If yes:

To health professionals YES NO Do not know

To patients YES NO Do not know

To donors YES NO Do not know

To other institutions, and/or companies

YES NO Do not know

If yes, to one of these, which kind of data?

b- Are there plans concerning information derived from the R&D based on the collection?

YES NO Do not know

If yes:

To health professionals YES NO Do not know

To patients YES NO Do not know

To donors YES NO Do not know

To other institutions, and/or companies

YES NO Do not know

c- Is material transfer agreement (MTA) used as a mean of implementing bioethical concerns??

- never
- from time to time
- always with some partners, but not with others
- most of the time
- always
- irrelevant because no use of MTA

1.12. Are the biobanking activities practiced in your company regulated by a legal framework?

YES NO Do not know

If YES,

a. Is this legal framework

National YES NO Do not know

European YES NO Do not know

International YES NO Do not know

b. Which level is most relevant according to your opinion?

National

European

International

c. Is it adapted to your activity in biobanking?

do not know ;

not at all adapted;

poorly adapted;

partially adapted;

rather well adapted;

fully adapted

1.13. Are bioethical issues in biobanking requiring the implementation of a new specific legal framework?

YES NO Do not know

If YES, what is the regulatory level you would consider most appropriate for your biobanking activity?

National YES NO Do not know

European YES NO Do not know

International YES NO Do not know

1.14. Are you using specific recommendations or good practices guidelines (soft law)?

Institutional YES NO Do not know

Professional YES NO Do not know

National YES NO Do not know

European YES NO Do not know

International YES NO Do not know

If YES, can you specify which ones or give the source: _____

12. ○ Other effect(s) ? YES NO Do not know

▪ If yes, which one(s)?

2.5.Does disclosure of R&D results raise bioethical issues?

| | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Never | Rarely | Rather often | Frequently | Always |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

If yes, please specify.

2.6.Are the cell/gene therapy activities practiced in your company regulated by a legal framework

Y/N /Do not know

If yes,

Is this legal framework:

| | | |
|----------------|-----|--------------|
| National? | Y/N | /Do not know |
| European? | Y/N | /Do not know |
| International? | Y/N | /Do not know |

a-Is this legal framework adapted to your activity in cell/gene therapy

- do not know ;
- not at all adapted;
- poorly adapted;
- partially adapted;
- rather well adapted;
- fully adapted

b- Are bioethical issues in cell/gene therapy requiring the implementation of a new specific legal framework?

YES NO Do not know

If yes what is the regulatory level you would consider most adequate for your cell/gene therapy activity?

| | | |
|---------------|-----|--------------|
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

c-Are you using specific recommendations or good practices guidelines⁷?

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |

⁷ Tick the right answer.

International Y/N /Do not know

If yes, can you specify which ones or give the source?

2.7 Is the regulatory category of the sample/product a source of concern?

YES NO Do not know Not applicable

If yes, it is:

Not very important concern

Important concern

Very important concern

2.8 Is the patentability of your products raising ethical issues for your company?

YES NO Do not know

If yes, please specify:

2.9 Is the commercialization of your products a source of bioethical concerns?

YES NO Do not know

3-Stem cell R&D

Is your company involved in Stem cells R&D?

YES NO Do not know

3.1 What type of stem cells are you working with?

o Stem cells from animals

YES NO Do not know

If yes,

Adult animal stem cells? YES NO Do not know

Embryonic animal stem cells? YES NO Do not know

o Stem cells from Humans

YES NO Do not know

If yes,

Adult human stem cells? YES NO Do not know

Embryonic human stem cells? YES NO Do not know

Embryonic stem cells lines? YES NO Do not know

Non embryonic stem cell lines? YES NO Do not know

3.2 In the case of human embryonic stem cells, what kind of use do you have?

- Fundamental research Y/N/ Do not know
- As industrial tools (tests, toxicology) Y/N/ Do not know
- Research aimed at future clinical application Y/N/ Do not know
- Other?
Please, Specify?

3.3 Conditions of production:

a- Do you foresee mass production of the products based on stem cells?

YES NO Do not know Not applicable

b- Do you use a bioreactor?

YES NO Do not know Not applicable

c- Do you use animal experimentation in the process of the product testing or production?

YES NO Do not know Not applicable

3.4 Associated data and registration of cell lines:

a- Do the data associated to the embryonic stem cells or stem cell lines allow to trace back the embryo source?

YES NO Do not know Not applicable

b- Are the cell lines part of a cell bank?

YES NO Do not know Not applicable

If yes, is it:

A national cell bank in your country?

A cell bank in another European country?

A cell bank in a non European country?

c- Are the cell lines registered in a registry outside your company?

YES NO Do not know Not applicable

If yes, is it:

A National Registry?

A European Registry?

An International Registry?

3.5 Are bioethical issues being raised by potential users of your products (for example, related to embryonic issues etc.)? Y/N /Do not know

- If yes, which issues and which users?

3.6 In the production process is there a particular technological step which raises ethical

issues? YES NO Do not know

If yes, please specify:

3.7 For use of biological material authorized, are bioethical issues raised in relation to access on such materials?

YES NO Do not know

If yes, please specify:

3.8 Are the stem cell activities practiced in your company regulated by a legal framework?

YES NO Do not know

If yes:

a-Is this legal framework ⁸

National? Y/N /Do not know

European? Y/N /Do not know

International? Y/N /Do not know

b-Is this legal framework

- Already implemented into your practice?

Y/N/partially /Do not know

- Is it adapted to your activity in stem cell R&D ⁹ €

c- Are bioethical issues in stem cell use requiring the implementation of a new specific legal framework? ¹⁰

Y/N /Do not know

If yes what is the regulatory level you would consider most adequate for your stem cell R&D activity?

National Y/N /Do not know

European Y/N /Do not know

International Y/N /Do not know

d-Are you using specific recommendations or good practices guidelines ¹¹?

⁸ Tick as appropriate.

⁹ Rank as : blank: do not know ; 0: not at all adapted; 1: poorly adapted; 2: partially adapted; 3: rather well adapted; 4: fully adapted;

¹⁰ Tick the right answer

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

If yes, can you specify which ones or give the source?

e-Is the regulatory definition of the category of the sample/product a source of concern?¹² Y/N /Do not know

¹¹ Tick the right answer.

¹² Rank as blank = do not know ; 0 : no concern; 1 : not an important concern; 2; important concern; 3: major concern

4 Diagnostics and related tests

Does your company develop an activity in diagnostics?

YES NO Do not know

4.1 What sort of tests do you develop?

Genetic diagnostic tests
Genetic susceptibility tests
Pharmacogenetic tests
Other biomolecular tests
Other, Please specify

4.2 Are there bioethical issues being raised by actual users of your tests?

Y/N/Do not know

- If yes, which issues and which users?

Tests assessment

Patentability

Information to patients

Choice of target populations

Decisions

Others, please specify

4.3 In your activity, are diagnostic/tests development practiced in your company regulated by a legal framework?

Y/N /Do not know

If yes,

Is this legal framework ¹³

| | | |
|----------------|-----|--------------|
| National? | Y/N | /Do not know |
| European? | Y/N | /Do not know |
| International? | Y/N | /Do not know |

a-Is this legal framework

- Already implemented into your practice?

Y/N/partially /Do not know

¹³ Tick as appropriate.

- Is it adapted to your activity in diagnostic/tests development activities ¹⁴
Y/N /Do not know

b- Are bioethical issues in diagnostic/tests development requiring the implementation of a new specific legal framework? ¹⁵

Y/N /Do not know

If yes what is the regulatory level you would consider most adequate for your diagnostic/tests development activity?

| | | |
|---------------|-----|--------------|
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

c- Are you using specific recommendations or good practices guidelines? ¹⁶

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

If yes, can you specify which ones or give the source

d- Are you aware of other existing recommendations in the diagnostic/tests development field? ¹⁷

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

○

If yes have you information on their source?

¹⁴ Rank as : blank: do not know ; 0: not at all adapted; 1: poorly adapted; 2: partially adapted; 3: rather well adapted; 4: fully adapted;

¹⁵ Tick the right answer

¹⁶ Tick the right answer

¹⁷ Tick the right answer

5- Nanobiotechnology

Is your company developing an activity in Nanobiotechnology?

YES NO Do not know

5.1 Nanotechnology Products:

Are your products used as a tool of toxicological studies? Y/N

Is the development of your product requiring specific toxicological studies? Y/N

Does manufacturing these nanoparticles imply an interface with living material? Y/N

Does the study of their characteristics imply an interface with living material? Y/N

5.2 Are there bioethical issues being raised by actual users of your products:

In terms of patentability of products Y/N /Do not know

In terms of clinical developments Y/N /Do not know

In terms of commercialization Y/N /Do not know

In terms of technology assessment Y/N /Do not know

If yes, which issues and which users?

5.3 Does the product's production process involve any stages of technological transformation? Y/N /Do not know

If yes, are these stages the source of bioethical issues?

Y/N /Do not know

Is there any link between the degree of advancement of production and the formal occurrence of bioethical questioning?

Y/N /Do not know

5.4 Does your work involve clinical trial? Y/N /Do not know

If yes, is the definition of target population for testing new drugs a source of bioethical concern?

Y/N /Do not know

5.5 Does the product's specific mode of action raise bioethical issues?

Y/N /Do not know

If, yes, is this related to:

Introduction of particles associated with specific risks? Y/N /Do not know

Violation of a person's privacy? Y/N /Do not know

Other effect(s) ? Y/N /Do not know

If yes, which one(s)?

5.6 Are the nanotechnology activities practiced in your company regulated by a legal framework?

Y/N /Do not know

If yes,

a-Is this legal framework¹⁸

National? Y/N /Do not know

¹⁸ Tick as appropriate.

| | | |
|----------------|-----|--------------|
| European? | Y/N | /Do not know |
| International? | Y/N | /Do not know |

b-Is this legal framework
Already implemented into your practice? Y/N/partially /Do not know

c-Is it adapted to your activity in nanotechnology¹⁹ Y/N/partially /Do not know

d- Are bioethical issues in nanotechnology requiring the implementation of a new specific legal framework?²⁰

Y/N /Do not know

If yes what is the regulatory level you would consider most adequate for your nanotechnology activity?

| | | |
|---------------|-----|--------------|
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

e-Are you using specific recommendations or good practices guidelines?²¹

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

If yes, can you specify which ones or give the source?

f- Are you aware of other existing recommendations in the nanotechnology field?²²

| | | |
|---------------|-----|--------------|
| Institutional | Y/N | /Do not know |
| Professional | Y/N | /Do not know |
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

o

If yes have you information on their source?

g- Is the regulatory definition of the category of the sample/product a source of concern?²³

Y/N /Do not know

¹⁹ Rank as : blank: do not know ; 0: not at all adapted; 1: poorly adapted; 2: partially adapted; 3: rather well adapted; 4: fully adapted;

²⁰ Tick the right answer for each point.

²¹ Tick the right answer.

²² Tick the right answer.

²³ Rank as blank = do not know ; 0 : no concern; 1 : not an important concern; 2; important concern; 3: major concern

6. CLINICAL TRIALS

Is your company sponsoring Clinical Trials?

YES NO Do not know

6.1 Tick the study type(s) you are sponsoring

Medicines testing
Cell and gene therapies
Tissue engineering
Cosmetics
Nutrition products
Medical equipment
Other medical equipment
Prosthesis or biomaterials
Surgical acts
Investigations with diagnostic aims
Pathophysiology
Psychological therapeutics
Other (please specify)

6.2 Give additional details on the type of study designs you are sponsoring

Paediatric studies
Adult studies
Orphan status

6.3 Is the definition of the target population an ethical concern?

Y/N /Do not know

6.4 In which therapeutic area are you carrying out clinical trials?

Cancer
Inflammatory diseases
Infectious diseases
Central Nervous System
Autoimmune diseases
Cardiovascular
Others, please specify

6.5 Do you face specific bioethical issues when you design your protocol of clinical trials?

Y/N /Do not know

If yes can you give details?

6.6 Have you established specific procedures for disclosing results of clinical trials?

Y/N /Do not know

6.7 Which level of legal framework do you refer to in your company?

National? Y/N /Do not know
European? Y/N /Do not know
International? Y/N /Do not know

a- Is this legal framework adapted to your activity

- do not know ;
- not at all adapted;
- poorly adapted;
- partially adapted;
- rather well adapted;
- fully adapted

b- Are bioethical issues in your activity requiring the implementation of a new specific legal framework?²⁴

Y/N /Do not know

If yes what is the regulatory level you would consider most adequate for your activity?

National Y/N /Do not know
European Y/N /Do not know
International Y/N /Do not know

c- Are you using specific recommendations or good practices guidelines²⁵?

Institutional Y/N /Do not know
Professional Y/N /Do not know
National Y/N /Do not know
European Y/N /Do not know
International Y/N /Do not know

If yes, can you specify which ones or give the source ?

d- To which body do you refer to for the protocols' ethical approval?

- National Ethics committee
- Local Research ethics committee
- Internal review board
- Other (please specify)

e- Do you find that the authorisation procedure established by the clinical trial EU directives is correctly implemented in your country?

- do not know ;
- not at all satisfied;
- poorly satisfied;
- partially satisfied;
- rather well satisfied;
- fully satisfied

²⁴ Tick the right answer.

²⁵ Tick the right answer.

f- Do you find the mechanism in place for the protocols' ethical approval?

- do not know ;
- not at all adapted;
- poorly adapted;
- partially adapted;
- rather well adapted;
- fully adapted

7. OTHER DOMAINS

7.1 Please specify the nature of your activity

7.2 Can you mention some ethical issues raising from your activity?

7.3 Are the activities practiced in your company regulated by a legal framework?
Y/N /Do not know

If yes,

a- Is this legal framework ²⁶

National? Y/N /Do not know

European? Y/N /Do not know

International? Y/N /Do not know

b- Is this legal framework

Already implemented into your practice?

Y/N/partially /Do not know

c- Is it adapted to your activity in nanotechnology ²⁷ €

d- Are bioethical issues in your activity requiring the implementation of a new specific legal framework? ²⁸

Y/N /Do not know

If yes what is the regulatory level you would consider most adequate for your activity?

National Y/N /Do not know

European Y/N /Do not know

International Y/N /Do not know

e- Are you using specific recommendations or good practices guidelines ²⁹?

Institutional Y/N /Do not know

Professional Y/N /Do not know

National Y/N /Do not know

European Y/N /Do not know

International Y/N /Do not know

If yes, can you specify which ones or give the source?

f- Are you aware of other existing recommendations in your field? ³⁰

Institutional Y/N /Do not know

Professional Y/N /Do not know

²⁶ Tick as appropriate.

²⁷ Rank as : blank: do not know ; 0: not at all adapted; 1: poorly adapted; 2: partially adapted; 3: rather well adapted; 4: fully adapted;

²⁸ Tick the right answer.

²⁹ Tick the right answer.

³⁰ Tick the right answer.

| | | |
|---------------|-----|--------------|
| National | Y/N | /Do not know |
| European | Y/N | /Do not know |
| International | Y/N | /Do not know |

If yes have you information on their source?

g- Is the regulatory definition of the category of the sample/product/technique a source of concern?³¹
Y/N /Do not know

³¹ Rank as blank = do not know ; 0 : no concern; 1 : not an important concern; 2; important concern; 3: major concern

8- Additional information as open questions (optional)

You can express below any additional comments or questions you may find useful to express regarding the bioethics-related practices in your company. Here are some topics you might find of interest to document.

Has the definition of the bioethical field as compared to legal framework and quality control been discussed in your company and did you come up with a definition of bioethics? In that case, can you give this definition?

Do you encounter difficulties in qualifying your products? Give examples.

Do you see bioethical questions as a serious obstacle to your activity; or as providing interesting opportunities? Give examples or details.

Is the European scale, or the broader international scale, raising different bioethical issues or difficulties as compared to your national situation? Can you give examples?

Are there activities you would foresee externalizing/relocating because of regulatory aspects?

Are there bioethical issues of relevance to your company that, to your knowledge, have not been addressed appropriately by a relevant ethics committee? Give examples.

Appendix 4 – Quantitative survey – List of companies targeted

| Number | Company Name | Activity | Survey Topic | Contacts | Function | Country |
|--------|------------------------------------|---|---------------------------------|----------------------------|-----------------------------|----------------|
| 1 | Active Biotech | Innovative substances that modulate the human immune system. MS & cancer | 1: Clinical Trials | Sven Andréasson | CEO | Sweden |
| 2 | Advancell | Exclusive platform of nanosystem technologies intended to the delivery of drugs, vaccines, genes | 3: Nanobiotech | Luis Ruiz | CEO | Spain |
| 3 | Asper | Genetic testing | 5: Diagnostics | Alo Merilo | Director | Estonia |
| 4 | BIO Invent International | Antibody based drugs in the fields of: Atherosclerosis, Thrombosis, Oncology, Ophthalmic diseases | 1: Clinical Trials | Svein Mathisen | CEO | Sweden |
| 5 | Bioalliance | Development of innovative therapeutics targeting drug resistance in cancer, HIV | 3: Nanobiotech/ Clinical trials | Gilles Avenard | COO | France |
| 6 | Biobank | Tissues databank | 4: Biobank | Pierre Lory | CEO | France |
| 7 | Biostatin | ovel signal transduction therapy agents | 1: Clinical trials | Dr. Szüts Tamás | CEO | Hungary |
| 8 | BTI Biotechnology Institute | Tissue engineering and bone regeneration | 2: Gene and cell therapy | Dr. Eduardo Anitua Aldecoa | CSO | Spain |
| 9 | Ceifer | Human fertility study and research, Assisted reproduction techniques, freezing of human fertility cells | 4: Biobank | Juan Pablo Ramírez López | CEO | Spain |
| 10 | Celecure | Pre-clinical development of anticancer drugs | 1: Pre-Clinical trials | Tarmo Kivi | CEO | Estonia |
| 11 | Cellartis | Drug discovery, toxicity testing, regenerative medicine on HES cells | 2: Stem cells research | Mats Lundwall | CEO | Sweden |
| 12 | Cellerix (Genetrix) | Medicines based on the use of adult origin stem cells, clinical trials | 2: Cell therapy | María Pascual | Clinic Development Director | Spain |

| | | | | | | |
|----|--|--|--|--------------------------------|------------------|----------------------|
| 13 | Celogos | Cell therapy company specialized in muscle regeneration | 2: Stem cells research | Christian Pinset | CSO | France |
| 14 | CeMines | Cancer Diagnostics | 5: Diagnostics | Richard Cavalli | CEO | USA (Estonia) |
| 15 | Codon | Autologous chondrocyte transplantation (ACT), and autologous disc derived chondrocyte transplantation (ADCT) | 2: Cell therapy | Dr. Olivera Josimovic-Alasevic | CEO | Germany |
| 16 | Competence Center for Cancer Research | Development of new generation cancer drugs, Cancer Diagnostics | 5: Diagnostics | - | - | Estonia |
| 17 | Diagnosticum Rt. | Diagnostic kits of clinical chemistry and immunology | 5: Diagnostics | Dr. Péterfy Ferenc | - | Hungary |
| 18 | Digna Biotech | Development and exploitation of the research products generated by the Center of Applied Medical Research (CIMA) | 1: Clinical Trials | Pablo Ortiz | General Director | Spain |
| 19 | DRC Kft | Phase I unit, Biochemical, Bioanalytical and Pharmacogenomics Laboratories, Out-Patient Clinics | 1: Clinical Trials Drug Research Center (DRC) | Dr. László Korányi | - | Hungary |
| 20 | Egeen | Clinical trials | 1: Clinical Trials | Kalev Kask | CEO | Estonia |
| 21 | Euroderm | In vitro skin models | 2: Tissue engineering | Andreas Emmendorffer | CEO | Germany |
| 22 | Fit Biotech (Quattromed) | DNA vaccination as well as in immuno- and gene therapies. | 2: Cell and Gene therapy | Kalevi Reijonen | CEO | Estonia |
| 23 | Genethon | Discovery & Development of Innovative gene therapy products for neuromuscular and immunologic genetic diseases treatment | 1: Clinical Trials 2: Gene & cell therapy 4: Biobank | Anne-Marie Masquelier | DG | France |
| 24 | Genodia | Detection of human pathogens by analysing their DNA or RNA library, genetic paternity tests | 5: Diagnostics | Béla Csókay | - | Hungary |

| | | | | | | |
|----|---|---|--------------------------------------|------------------------------------|----------|-----------------------------|
| 25 | GenoID Kft | Developpement of Diagnostic kits targeting infectious or genetical diseases +Drug discovery services | 5:Diagnosics | Dr. Csaba Jeney | - | Hungary |
| 26 | Hisztopatológia Kft. | Sells a broad range of monoclonal antibodies and diagnostic products | 5:Diagnosics | Dr. Szekeres György | - | Hungary |
| 27 | Ibimer (Granada University) | Public research center in immunology and cancer | 2: Gene therapy | Dr. José Mariano Ruiz de Almodóvar | - | Spain |
| 28 | IDM | Innovative products that activate the immune system to treat cancer. | 2: Cell therapy | Jean-Loup Romet-Lemonne | CEO | France |
| 29 | Indas Biotech | Kits for diagnosis, prognosis and/ or response to cancer treatment, to cardiovascular and neurodegenerative diseases | 5: Diagnosics | José-Cándido Arochena Amestoy | CEO | Spain |
| 30 | Innate pharma | Develops drugs targeting the innate immune system. | 1: Clinical Trials | Hervé BRAILLY | CEO | France |
| 31 | Innogenetics | Diagnostics business focusing on infectious diseases, genetic testing, neurodegeneration | 5:Diagnosics | - | - | Belgium |
| 32 | Institut des cellules souches (I-STEM) | ESC, cell therapy | 2:Cell therapy | Dr. Marc Peschanski | Director | France |
| 33 | Integragen | Innovative products (diabetes) & services (genotyping) | 5:Diagnosics | Jan Mous | CEO | France |
| 34 | Intelligent Medical Implants | Retinal Implants: visual prosthesis - an "artificial retina" | 3: Nanobiotech | Stephan Rietiker | CEO | Germany/ Switzerland |
| 35 | Ipsogen | Molecular tools for , to predict patient response to treatment | 5:Diagnosics | Vincent Fert | CEO | France |
| 36 | KaroBIO | Drug discovery and development company specializing in nuclear receptors with focus on metabolic diseases, in-house preclinical development | 1: Clinical Trials (too early stage) | Per-Olof Wallstrom | CEO | Sweden |

| | | | | | | |
|----|------------------------------|---|-------------------------|---------------------------|---------------------------------|----------------|
| 37 | Karolinska Institutet | Stem cell biology and adult neurogenesis | 2:Gene and cell therapy | Jonas Frisé | Professor in Stem Cell Research | Sweden |
| 38 | Kelen Kórház Kft | Private hospital | 2:Cell therapy | - | - | Hungary |
| 39 | KPS Biotechnology Ltd | Drugs discovery, diagnostics, cell therapy | 2:Cell therapy | Istvan Petak | CSO | Hungary |
| 40 | KTH | Royal Institute of Technology | 3:Nanobiotech | Helene Andersson | Research leader in Nanobiotech | Sweden |
| 41 | Laboratorios LETI | Immunology and preventive medicine, diagnostic products and self-health care | 5: Diagnostics | Gloria Roé | - | Spain |
| 42 | Myosix (Genzyme) | Expertise in muscle cell therapy for development of cell-based therapeutics. | 2: Stem cells research | Erik Tambuyzer | Vice President | Belgium |
| 43 | Nanobiotix | Develops NanoBiodrugs targeting cancer | 3: Nanobiotech | Laurent Levy | CEO | France |
| 44 | Neocodex | Tumor databank | 4: Biobank | Enrique Vázquez Tatay | Director | Spain |
| 45 | Neuro Axis | Products targeting neuro-endocrine and immune system disorders, neurodegenerative diseases. | 5:Diagnosics | Françoise Touraine Moulin | - | Canada |
| 46 | Neuronova | Substances enhancing neurogenesis | 2:Cell and gene therapy | Anders Haegerstrand | CEO | Sweden |
| 47 | Neuropharma (Zeltia) | Focuses on Alzheimer's disease. Preclinical trials in 2005. | 1: Clinical Trials | Carmen Eibe | Director | Spain |
| 48 | N-Gene Kft | Pipeline of drugs treating insulin-resistance | 1:Clinical Trials | Dr. Péter Literáti Nagy | - | Hungary |
| 49 | NSCRI | Clinical research Institute | 1:Clinical trials | Bengt Furberg | Chairman of the board | Sweden |
| 50 | Oryzon | Human molecular diagnostics | 5: Diagnostics | Carlos Buesa | General Director | Spain |

| | | | | | | |
|----|---------------------------|---|------------------------|----------------------|-------------------|----------------|
| 51 | Phadia | Blood test systems to support clinical diagnosis, monitoring of allergy, asthma | 5: Diagnostics | Magnus Borres | Secretary General | Sweden |
| 52 | Pharmamar (Zeltia) | Development of marine derived antitumoral agent. Products from preclinical to phase III | 1: Clinical Trials | Carmen Eibe | Director | Spain |
| 53 | Protobios | Biomedical research for diagnostic and therapeutic purposes. | 2: Stem cell | Jaanus Pikani | Chairmanship | Estonia |
| 54 | Quattromed | Molecular Diagnostics and pharmaceutical research | 5: Diagnostics | Erki Mölder | CEO | Estonia |
| 55 | Reneuron | Stem cell platform technology: stroke, diabetes... | 2: Stem cells research | Michael Hunt | CEO | UK |
| 56 | Sejtbank Kft. | Biobank | 4: Biobank | - | - | Hungary |
| 57 | SeroScience kft | Specializes in preclinical research to identify, predict and prevent complement-activation related infusion reactions. | 5: Diagnostics | Dr. Peter Krajcsi | - | Hungary |
| 58 | Sistemas Genómicos | DNA applications | 5: Diagnostics | José Carlos Monforte | - | Spain |
| 59 | Solvo Rt | Fields ATP binding cassette), transporters playing a role in multidrug resistance of malignancies, developing therapeutics, diagnostics and drug discovery assays | 5: Diagnostics | Pr. Erno Duda | CEO | Hungary |
| 60 | TCLand | Innovative immunological biomarkers and therapies for unmet medical needs in transplantation and auto-immune diseases. | 2: Cell therapy | Alain Huriez | CEO | France |
| 61 | ThalèsNano Ltd | Developing and providing microscale flow instruments | 3: Nanobiotech | - | - | Hungary |
| 62 | Tigenix | Development of innovative treatments for | 2: Cell therapy | Gil Beyen | CEO | Belgium |

| | | | | | | |
|----|---------------------|--|------------------------|----------------------|----------|----------------|
| | | damaged and osteoarthritic joints | | | | |
| 63 | Transgene | Therapeutic vaccines, immunotherapy for treatment of cancer and infectious diseases. | 2: Gene therapy | Philippe Archinard | DG | France |
| 64 | Trio-Lab Kft | Therapeutic methods based on culture of autologues cells, Skin bank (chronic skin disorders) | 4: Biobank | Dr. Norbert Nagy | CEO | Hungary |
| 65 | TxCeLL | New therapies to cure inflammatory and autoimmune diseases with regulatory T cells | 2: Cell therapy | Frédéric HAMMEL | CEO | France |
| 66 | Vaxon | Immunotherapy against cancer | 2: Cell therapy | Kostas Kosmatopoulos | CSO | France |
| 67 | Vidacord | Ombilical cells | 2: Stem cells research | Angel Alvarez | Director | Spain |
| 68 | Zelion | Biobank | 4: Biobank | - | - | Hungary |