Biomanufacturing in France

France Biotech's Survey - Fall 2003

- October 2003 -

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Introduction

Since its creation in the late 70's, the biotech industry has adopted its own business models, its own R&D approaches and its own financial system, all of them different from that of the classical pharmaceutical industry. This revolution was linked to new types of products that came out from biotech labs, and to new ways of designing them. When big pharmas were developing merely chemical-based drugs, biotechs were searching for biological-based treatments. These treatments have led to the elaboration of new biochemical entities (monoclonal antibodies, recombinant proteins, plasmid DNA, viruses, etc.) that were chemically much more complex than traditional small molecules.

Thus, not only have the products changed, but also the manufacturing process. The processes designed to produce biotech products usually comprise a natural bio-engineering phase that takes place in a living organism. Therefore, while pharmaceutical processes deal with chemistry, biotech processes are aimed at breeding living systems and "milking" them. Understandably, this led to the development of new industrial processes designed to meet biotech's needs. By now, the biological-based manufacturing industry is well-established and has completely integrated this new way of producing drugs.

Even if the manufacturing aspects have been somewhat hidden by the research itself (pharmaceutical research and clinical research), which was put under the spotlight by both the academic and the financial world, many companies that can be called "bio-manufacturers" have emerged. Thanks to the dynamic of its biotech sector, the first country that has logically hosted a significant number of bio-manufacturers is the USA. However, since the early 90's this industry has also surfaced in certain European countries such as the UK and Germany.

As a matter of fact, Bio-manufacturing is a growing sector, and according to a recent JP Morgan[1] study, production capacities should be saturated in the very coming years. This growth has been even unpredictably boosted by the terrorist attack of September 11^{th,} 2001 on New York City's Twin Towers and the bio-terrorism threat, which have led governments to mass-produce new vaccine versions against classic pathogens.

In this context, France Biotech wanted to establish France's position in the big picture. Certainly, Bio-manufacturing has not been a major focus in France, where means and energies have been directed to constitute patent portfolios. However, to have a more accurate view of the market, of its actors, of its needs and trends, France Biotech launched a national enquiry on bio-manufacturing.

This report recapitulates the findings of the study. It is organized as follows:

- Presentation of the context
- Description of the methodology
- Analysis of data,
- Drawing of the key-trends and
- Recommendations.

[1] Molowa, D. The State of Biologics Manufacturing, JP Morgan Securities Inc., New York : March 12, 2001

A. Context and methodology

A.I. On Biomanufacturing

Introduction

The biotech industry which emerged in Europe more than twenty years ago has not yet led to the development of large manufacturing facilities. Existing production sites in most cases aim at producing each company's own products. Subcontracting the manufacturing process is not yet fully entered in the biotech sector's culture --like it already has in other industries. Nevertheless, new attitudes are surfacing whereby more and more companies are ready to release their manufacturing capabilities and their know-how to meet other players' production needs in partnering relationships.

But prior to entering into the detail of France Biotech's study, we need to define the term "Biomanufacturing".

What is Biomanufacturing?

Biomanufacturing is the performance for an external client within a contractual framework of a large-scale validated process, that necessitates biotechnological steps and/or leads to the production of biological material or products directly issued from biological materials –within the pharmaceutical, vaccine and diagnostics industries.

While "Biomanufacturing" covers different types of activities, the above definition draws a clear line between research and production. Research aims at discovering new genes, molecules or proteins, rather than setting reliable processes for mass-producing them.

Bioengineering technologies which are used and often provide the basis for biotechnological research can be nonetheless an integral part of a biomanufacturing process.

A.II. Methodology

The goal of France Biotech's study was to get an accurate depiction of Biomanufacturing in France today. This means identifying the actors (clients and suppliers), their needs and their mode of operation (technically, economically and legally).

As far as we know, no study on Biomanufacturing in France has been published until today. Therefore, the way to proceed was to carry out the study on our own, taking advantage of France Biotech's membership directory. After discussion, it was decided to set-up a questionnaire, in order to get "new" data and for processing.

Indeed, the questionnaire was addressed to all the members of France Biotech. After several telephone requests in July and August, 30 usable questionnaires were received, in particular from the companies most advanced in their research.

In addition, for reasons related to the confidentiality of their projects, 30 other companies or subcontracting companies at an early stage of their research did not wish to answer our questionnaire.

The first results of the analysis were submitted at a France Biotech Biomanufacturing Study Steering Committee to collect opinions and comments.

Below are the various phases required to achieve the study:

Phase I: write-up and validation of the questionnaire
Write-up of a draft questionnaire
Validation within France Biotech
Beta-testing with selected members

Phase II: data collection
Definition of a sample
Data collection

Phase III: data processing
Analysis of the data
Writing of a report

A.III. Phase I: write- up and validation of the questionnaire

Having no previous survey, the questionnaire had to be designed from scratch, taking into account the extreme diversity of the biotech industry. Diversity occurs in terms of product types, product application, production mode and quantities. While aiming to be as exhaustive as possible, we could not take into account each company's specificity if we wanted to remain significant. Therefore, we decided to check off the companies that were not working in human health, i.e. companies that were out of the diagnostics, therapeutics or vaccine fields. This restriction on the study scope allowed us to draft the questionnaire, and we proposed to split the questions into four parts: general questions, production, quality control and sector-specific questions.

Once written, we submitted the draft to several French biotech managers as beta-testers. They made remarks and comments and helped us write the last part or the questionnaire (the sector-specific part). See appendix 1 for questionnaire.

A.IV. Phase II: data collection

To get statistical data that could be processed, we had to define a sample size. After discussion, we decided that having half of France Biotech's members answering the questionnaire --i.e. thirty answers-- would be significant enough to complete the study.

Though biotech managers were often reluctant about answering the questionnaire, in most cases we nonetheless reached our objective of thirty answered questionnaire. They said that some questions were too confidential to be answered thus complicating and delaying the analysis.

This phase lasted four months, from April to August, 2003.

A.V. Phase III: data processing

Data was processed using the results of the enquiry. We removed the sector-specific questions that were considered too confidential to be analyzed by most biotech managers. Answers were not always provided thus**…**the representativeness of the sample.

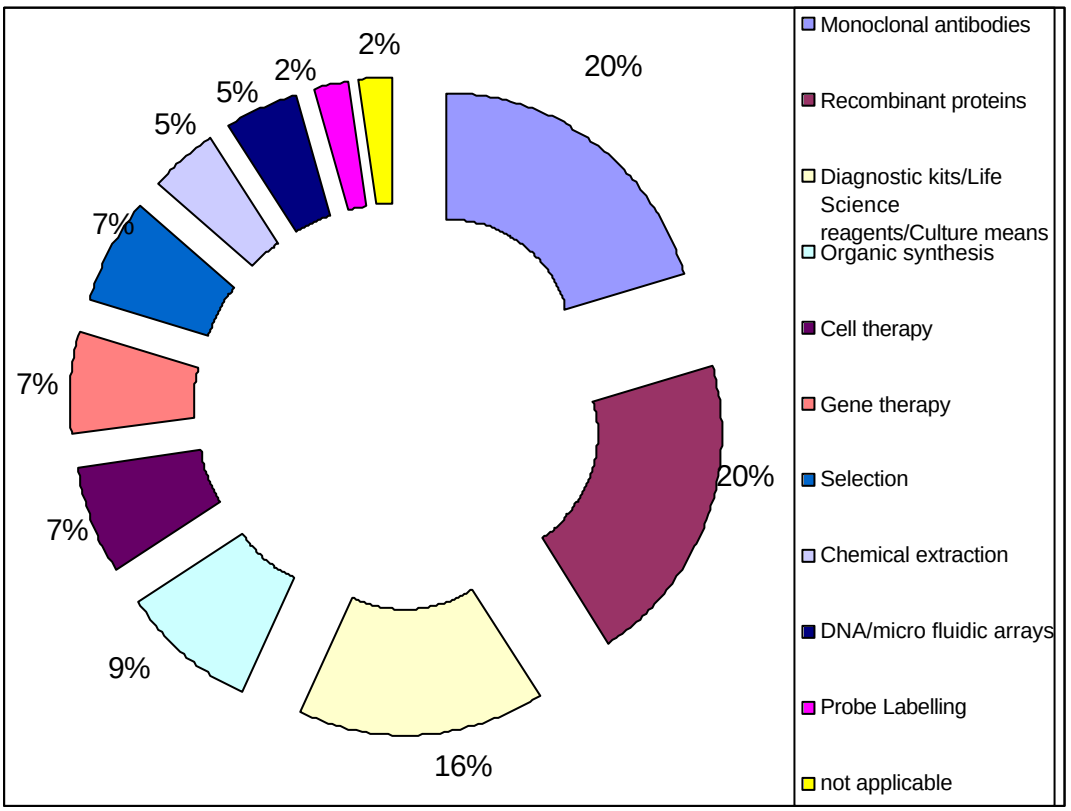
B. Data Analysis

The collected data is displayed as a circle histogram graph. However, due to the small number of participants and the frequent lack of answers to some questions, the percentage histogram will be displayed as well as the raw data for reference. The total number of answers to each question is displayed at the end of each table. In some cases, the total is superior to 30 (>30) as a consequence of applicants giving more than one answer.

B. I General Questions

QUESTION N° 1: WHAT SCIENTIFIC APPLICATION(S) ARE YOU WORKING ON?

Scientific applications	Number of answers
Monoclonal antibodies	9
Recombinant proteins	9
Diagnostic kits/Life Science reagents/Culture means	7
Organic synthesis	4
Cell therapy	3
Gene therapy	3
Selection	3
Chemical extraction	2
DNA/micro fluidic diagrams	2
Probe Labelling	1
Not applicable	1

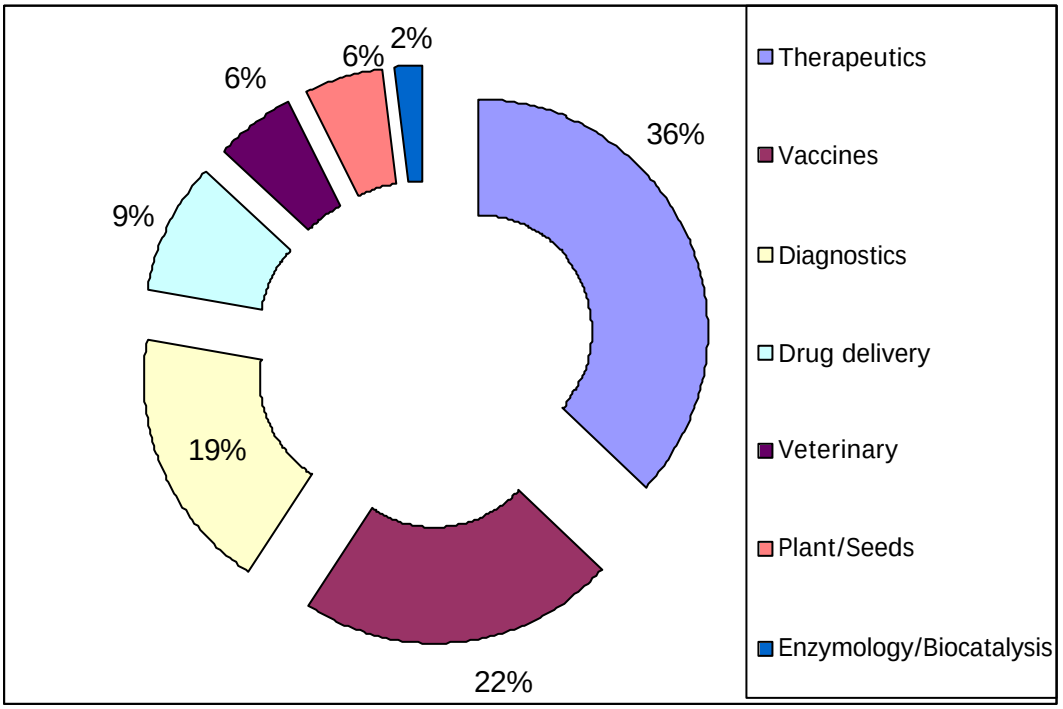


This first diagram shows the repartition of companies according to their scientific applications. Three main groups can be identified:
- First group: **peptide-based technologies** (monoclonal antibodies and recombinant proteins), represent together 40% of the scientific applications.
- Second group: **diagnostics kits and research tools** represent 16% of the total.
- Third group: **cell and virus-based technologies** (cell therapy and gene therapy) total 14% of the scientific applications.
- Fourth group: **chemical extraction** which is not specific to the biotech industry still represents 9% of the scientific applications.

Peptide-based technologies are the most widely-spread among the French biotechs. This result is consistent with the only biotech pharmaceutical products that have already reached the market. In most cases, they are either monoclonal antibodies or recombinant proteins. Conversely, gene and cell therapy, which relate to more recent scientific findings are still less mature.

QUESTION N° 2: WHAT IS YOUR DOMAIN OF ACTIVITY?

Domain of activity	Number of answers
Therapeutics	20
Vaccines	12
Diagnostics	10
Drug delivery	5
Veterinary	3
Plant/Seeds	3
Enzymology/Biocatalysis	1

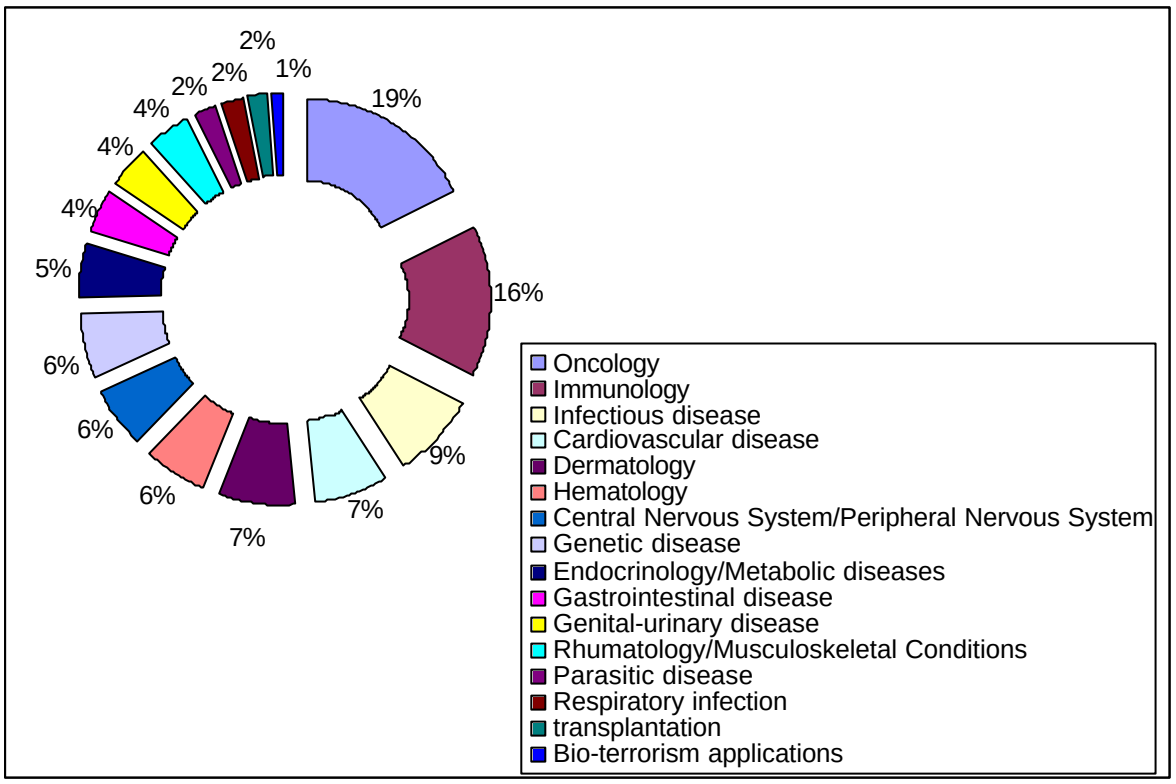


Regarding the activity domain, two main groups can be isolated:
- First group: therapeutics and vaccines representing together 58% of the total.
- Second group: diagnostics kits, representing 19% of the total.
Other domains are minor.

In terms of biomanufacturing, this diagram shows that 58% of the French biotech is going to go through the classic clinical phase process, and need to have products that require a high-level of safety.

QUESTION N° 3: IF YOUR PRODUCT(S) CONCERN(S) HUMAN HEALTH, WHAT THERAPEUTIC DOMAIN(S) ARE YOU FOCUSING ON?

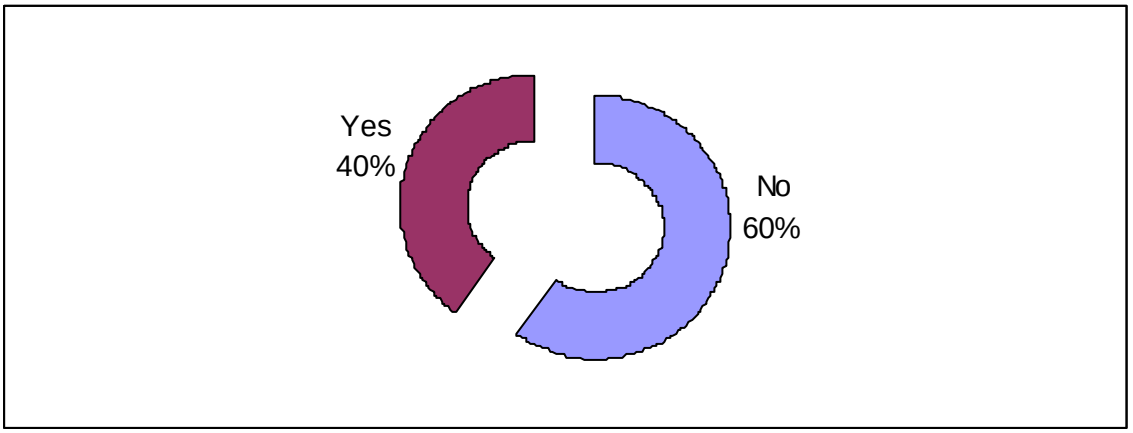
Therapeutic domain	Number of answers
Oncology	17
Immunology	14
Infectious disease	8
Cardiovascular disease	7
Dermatology	7
Hematology	6
CNS	6
Genetic disease	6
Endocrinology/Metabolic diseases	5
Gastrointestinal disease	4
Genital-urinary disease	4
Rhumatology/Musculoskeletal Conditions	4
Parasitic disease	2
Respiratory infection	2
Transplantation	2
Bio-terrorism applications	1
All domains concerned by fermentation	1
Recombinant proteins/all therapeutics applications	1
Cell quality	1
Not specialized in a particular domain	1
Not applicable	2
Not answered	5



Apart from oncology and immunology which cover a significant percentage of French biotech therapeutic domains, any other medical application is almost equally covered. In terms of corresponding production techniques, the disparity is not large, in that techniques are mostly identical in all medical fields. This diagram is rather commercially significant. Due to the disparity of domains represented, finding (or identifying) a client or a supplier for manufacturing applications requires looking beyond one's therapeutic specialty which can sometimes be hindrance. In response to this observation and to facilitate partnering, a centralized structure that would gather supply and demand for bio-manufacturing could be helpful.

QUESTION N° 4: DO YOU ALREADY HAVE A PRODUCT(S) ON THE MARKET?

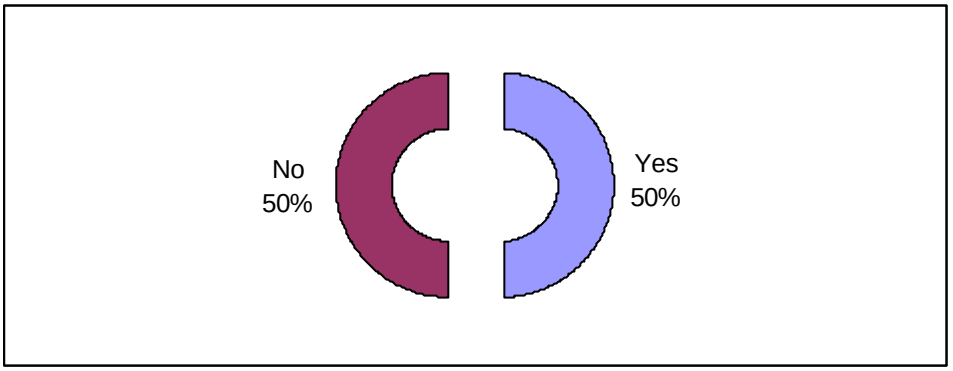
	Number of answers
No	18
Yes	12



40% of French biotechs claim that they have a product on the market. By looking more closely, most of them are acting in the diagnostics/research tools industry, where the setting-up of new product is much quicker than in the therapeutics field. (Does not require a market authorization)

QUESTION N°5 DO YOU MANUFACTURE YOUR PRODUCT(S) INTERNALLY ?

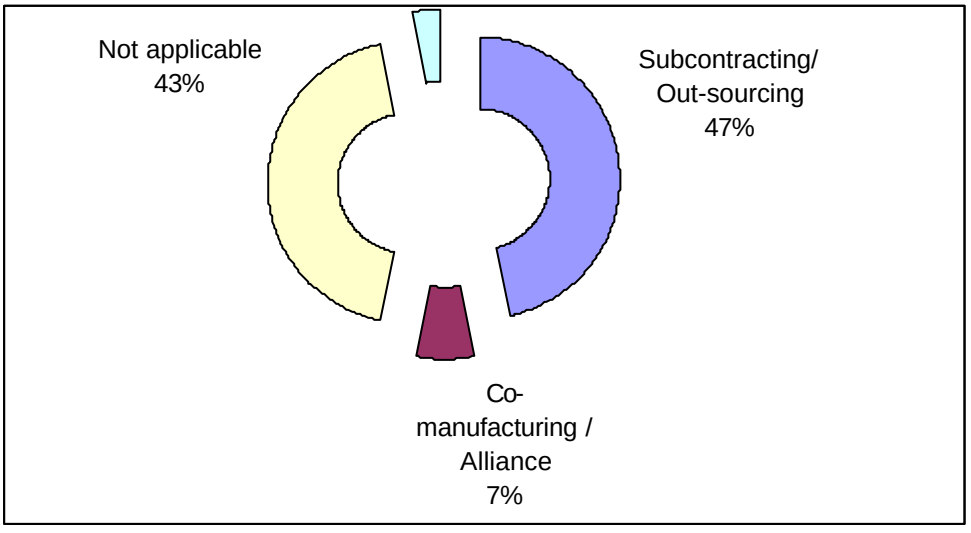
	Number of answers
Yes	15
No	15



The fifty-fifty kind of answer to this question shows that a high percentage of biotechs are aware that R&D and manufacturing are two separate functions. However, depending on the type of products, some of them are providing their own manufacturing.

QUESTION N°6: IF YOU ANSWERED "NO" TO QUESTION N°5, HOW DO YOU MANUFACTURE YOUR PRODUCT(S)?

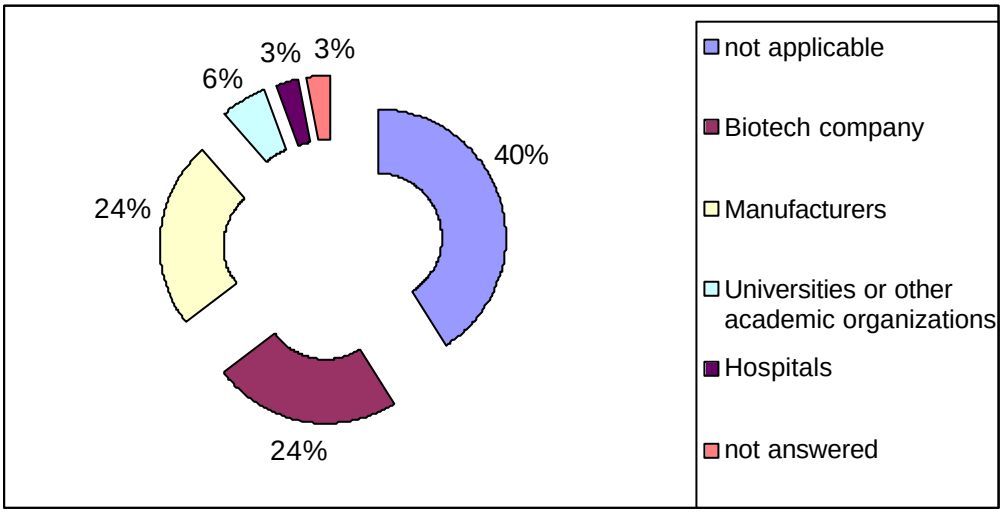
Manufacture mode	Number of answers
Subcontracting/Out-sourcing	14
Co-manufacturing / Alliance	2
Not applicable	13
not answered	1



In case they would solicit an external bio-manufacturer, the large majority of biotechs would consider it as a pure service provider (93%). Actually, due to the upcoming lack of manufacturing capabilities, it would not be surprising if manufacturers would not accept this kind of relationship in the future. They might be directly associated to the success of the product and therefore be willing to set-up an alliance.

QUESTION N°7: IF YOU ANSWERED "NO" TO QUESTION N°5, WHAT TYPE OF MANUFACTURING PARTNER(S) HAVE YOU BEEN WORKING WITH?

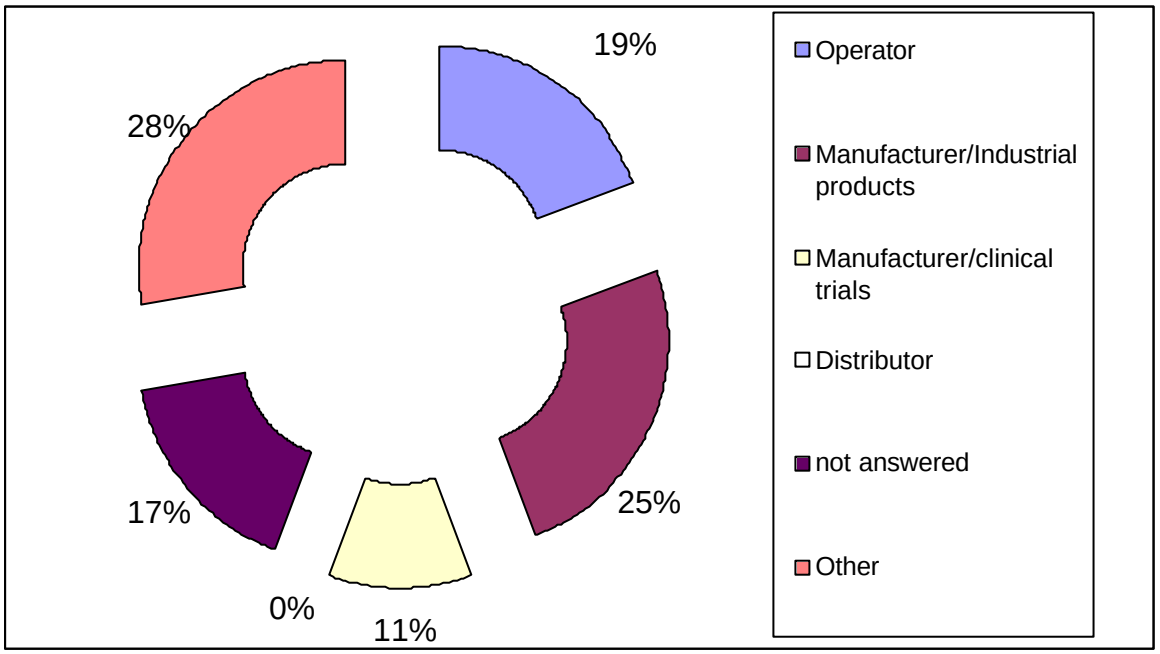
Type of manufacturing partners	Number of answers
not answered	1
Biotech company	8
Manufacturers	8
not applicable	14
Universities or other academic organizations	2
Hospitals	1



More than half of participants did not answer this question, showing that a large proportion of participants do not consider biomanufacturing as a current priority. But, the participants, who have answered this question, seem very conscious of biomanufacturing constraints, and would choose a professional subcontractor rather than an academic organization to sign a biomanufacturing deal.

QUESTION N°8: WHAT TYPE OF STRUCTURE DOES YOUR COMPANY POSSESS?

Company's structure	Number of answers
Operator	7
Manufacturer/industrial products	9
Manufacturer/clinical trials	4
Distributor	0
not answered	6
Other	10

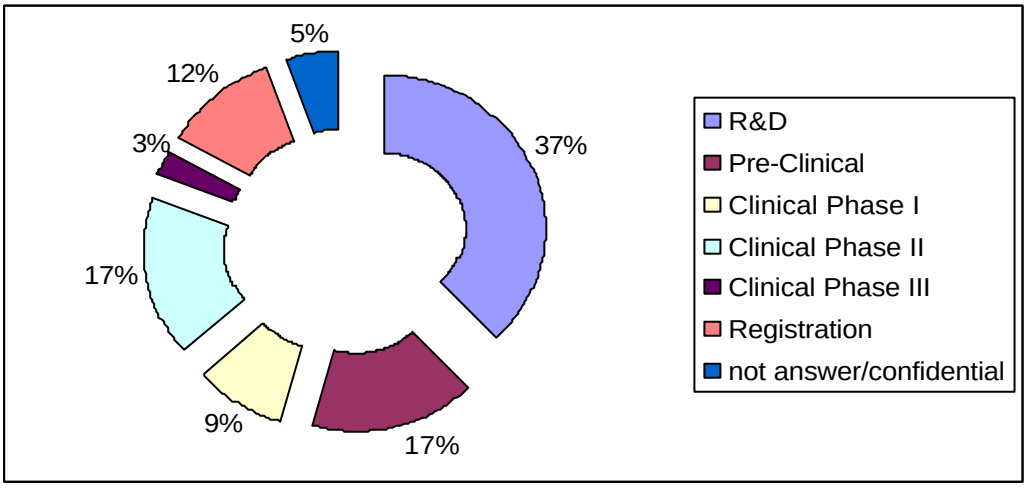


This question is not easy to interpret because of the large number of participants which did not recognize themselves in the listed categories. But more than 35% (manufacturer categories) are already aware of biomanufacturing aspects.

B.II. Production

QUESTION N° 9: AT WHICH PHASE OF DEVELOPMENT IS(ARE) YOUR PRODUCT(S) CURRENTLY POSITIONED?

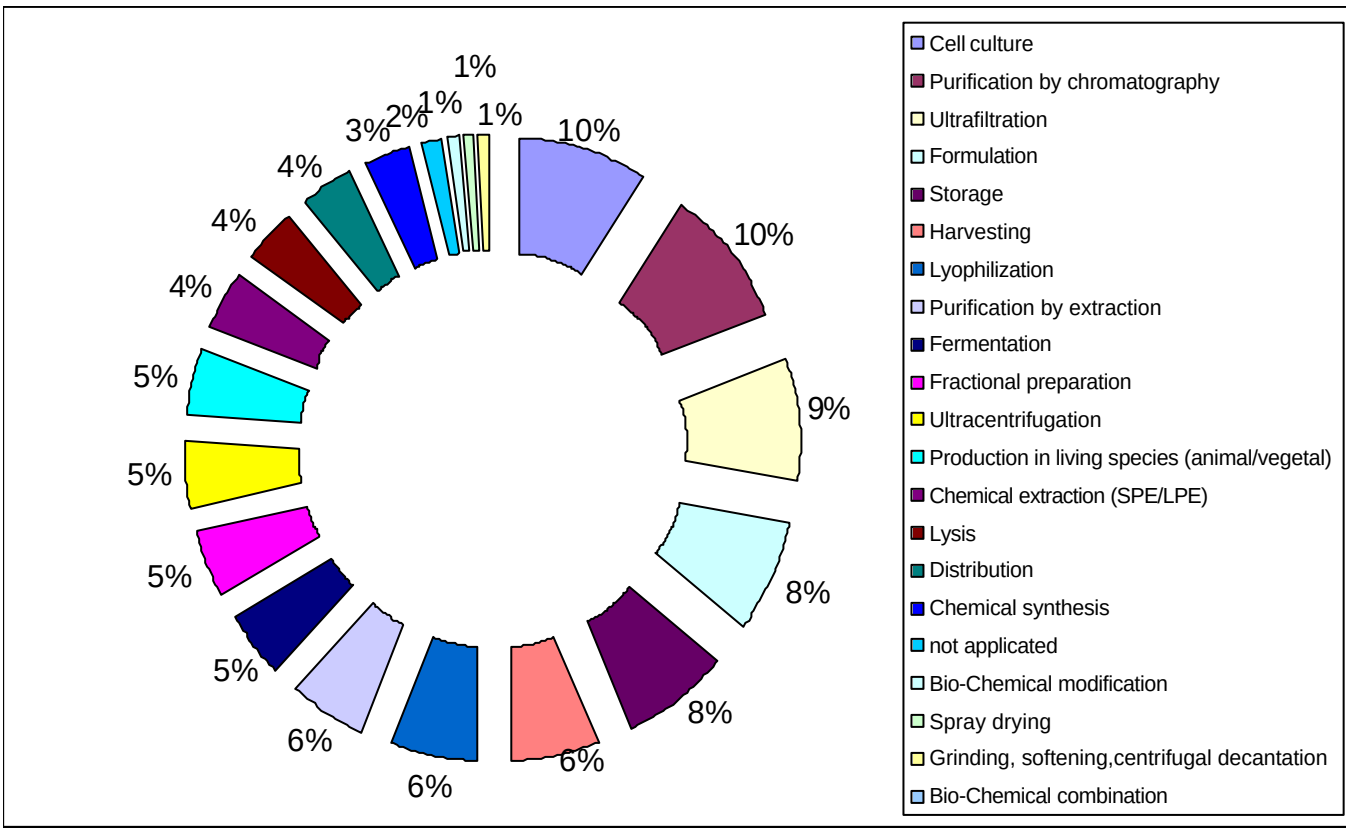
Development phase on 77 Candidates name	Number of answers
R&D	29
Pre-Clinical	13
Clinical Phase II	13
Clinical Phase I	7
Registration	9
Clinical Phase III	2
Not answered/confidential	4



Logically, the number of products decreases according to their stage of development. However, there are two products in Phase III and 9 awaiting registration. If we take into account all products from clinical Phase I to registration that are being manufactured, we arrive to a total of 31. Those 31 products can already be considered as a potential biomanufacturing market for subcontracting.

QUESTION N°10: WHICH TECHNICAL STEPS (IN-HOUSE OR SUBCONTRACTED) ARE REQUIRED TO MANUFACTURE YOUR PRODUCT ON A LARGE SCALE?

Technical steps	Number of answers
Cell culture	12
Purification by chromatography	12
Ultrafiltration	11
Formulation	10
Storage	10
Harvesting	8
Lyophilization	8
Purification by extraction	7
Fermentation	6
Fractional preparation	6
Ultracentrifugation	6
Production in living species (animal/vegetal)	6
Chemical extraction (SPE/LPE)	5
Lysis	5
Distribution	5
Chemical synthesis	4
Bio-Chemical modification	1
Spray drying	1
Grinding, softening,centrifugal decantation	1
Bio-Chemical combination	0
Not applicable	2



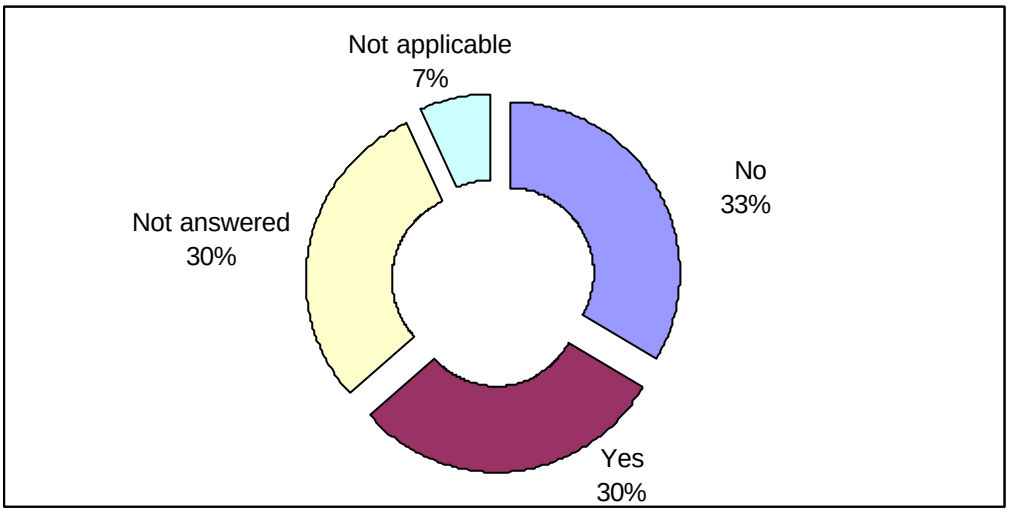
The answer to this question clearly shows the extreme breadth of technologies used by the biotech industry. Clearly no contract manufacturing organization (CMO) could claim that they are able to manage all technologies listed. This question gives an insight of what will be the future biomanufacturing market: It will be a segmented market, where each actor will be specialized in certain technologies.

QUESTION N°11: WHAT QUANTITIES HAVE YOU PRODUCED OR ARE YOU PLANNING TO PRODUCE FOR EACH CLINICAL PHASE?

Most of the biotech managers were not willing to answer this question. Therefore, no sufficient data has been collected to complete an analysis.

QUESTION N°12: HAVE YOU ALREADY PERFORMED A SCALE-UP OF YOUR PRODUCTION?

Scale-up	Number of answers
No	10
Yes	9
Not answered	9
Not applicable	2

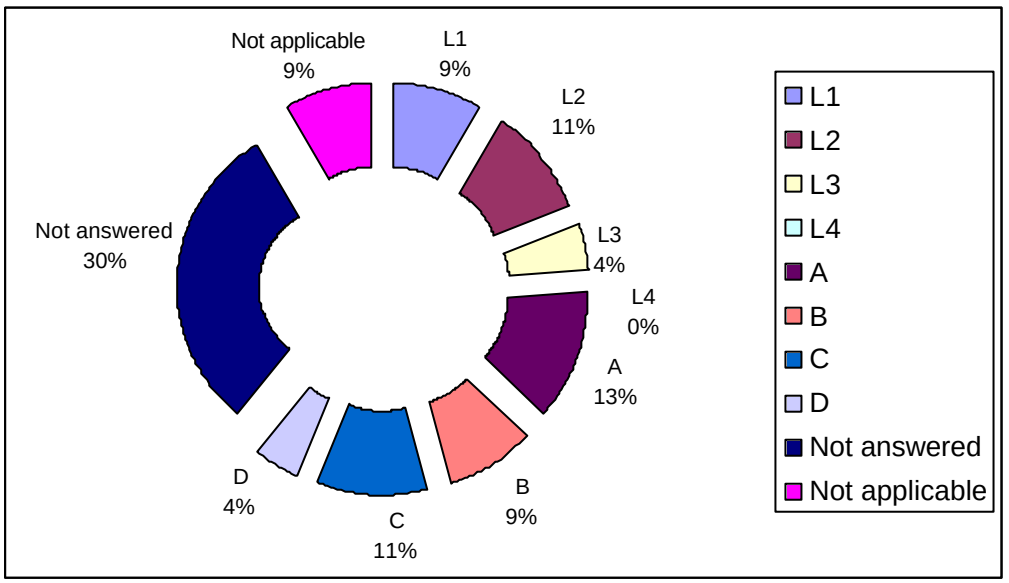


The answers to this question are a bit ambiguous in the sense that "*no*", "*not applicable*" and "*not answered*" can be interpreted variously. Through discussions with biotech managers:
- "*no"* means that the answerer has not yet performed any scale-up but knows he will have to.
- "*Not answered"* means that he has not yet thought about it, the product being too far from being marketable.
- "*Not applicable*" means that he will not have to think about it, the product or service is not mass-produced.

This being explained, we can see that more than 60% have no idea yet of the way to mass-produce their products. On the one hand, this undoubtedly shows some immaturity on the part of the biotech industry in France. On the other hand, the "*Yes*" + "*No*" answers represent 63% of the total and correspond to the potential biomanufacturing market which is a significant percentage.

QUESTION N°13: WHAT IS THE SUITABLE CONFINEMENT LEVEL REQUESTED BY REGULATORY AUTHORITIES?

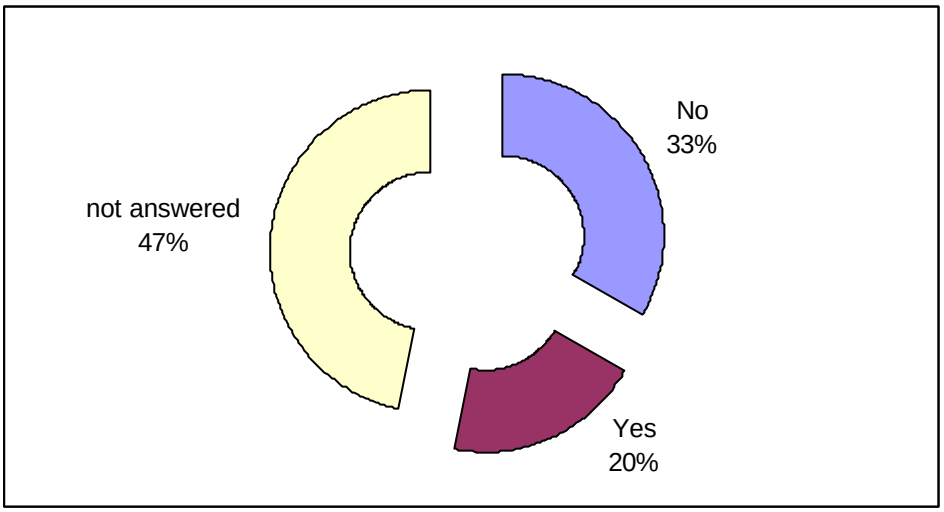
Confinement level	Number of answers
L1	4
L2	5
L3	2
L4	0
A	6
B	4
C	5
D	2
Not answered	14
Not applicable	4



Regarding viral confinement, all answers are around 10%, apart from L3 and L4. L4 represents 0% which is not surprising given the very few L4 classified labs in the world. More interesting is the low level of L3 labs (4%) which means that few biotechs work with dangerous viruses (such as HIV) for human beings. In terms of particle count, requirements are almost equivalent for A, B,C categories (low level of confinement). High-level of confinement is rarely required (D categories: 4%), which is consistent with the results obtained with the viral classification. This equal repartition already suggests a segmentation in terms of biomanufacturing. As a matter of fact, only some companies, which are already approved for certain types of operations, could perform the same operations for a partner according to confinement regulation issues.

QUESTION N°14: CAN YOU ESTIMATE THE SIZE OF EQUIPMENT REQUIRED FOR THE PRODUCTION OF A PHASE X LOT? CAN YOU QUANTIFY THE YIELD OF THE FINAL MATERIAL THAT WOULD BE PRODUCED WITH THIS EQUIPMENT?

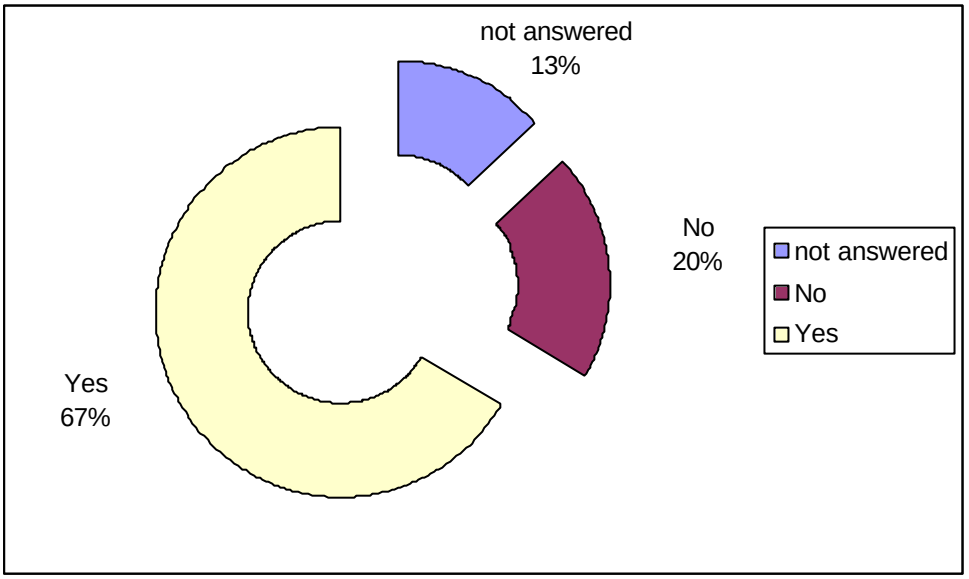
Size of equipment	Number of answers
No	10
Yes	6
Not answered	14



According to this graph, only one company out of five is able to estimate its needs in term of production equipment. This is a sign of misreading one's needs and market immaturity in planning for clinical development. The finding is corroborated by the total absence of answers regarding the yields.

QUESTION N°15: DO YOU HAVE ANY CONSTRAINTS REGARDING THE MANUFACTURING FACILITY (DEDICATED, MULTI-USE, MULTI-PURPOSE, GMP COMPLIANCE ETC…)?

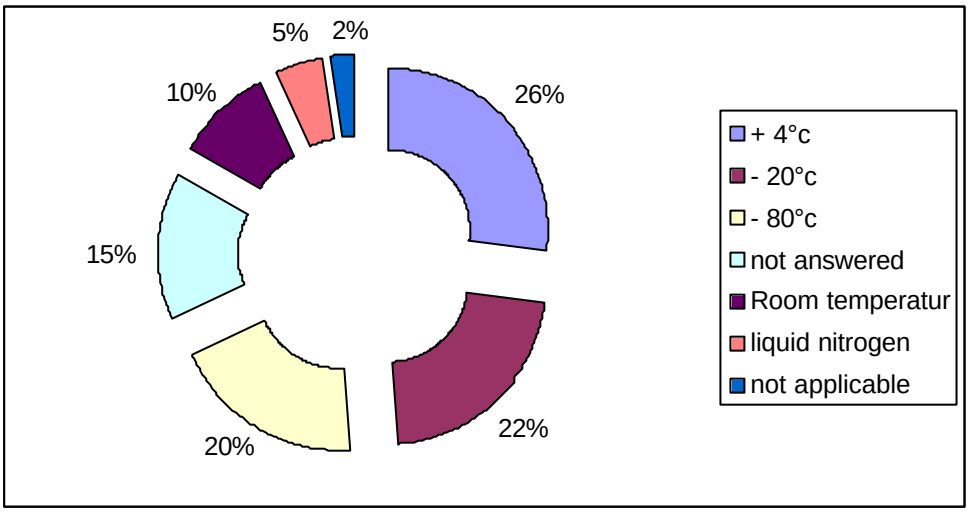
Manufacturing facility constraints	Number of answers
No	6
Yes	20
Not answered	4



Most companies are aware of manufacturing regulations, even if they are not producing yet.

QUESTION N°17: AT WHAT TEMPERATURE(S) ARE YOU STORING YOUR PRODUCTS?

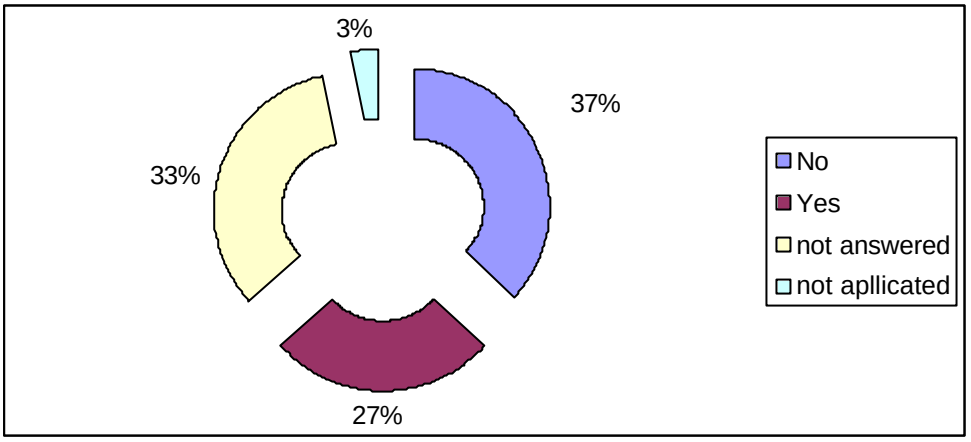
Storage temperature	Number of answers
+ 4°C	11
- 20°C	9
- 80°C	8
Not answered	6
Room temperature	4
Liquid nitrogen	2
Not applicable	1



In most cases, products are stored at room temperature, +4°C and -20°C (in 58% of the cases). This means that storing is not a major issue in terms of biomanufacturing, in that even -20°C storing is very common in labs today. A quarter of the compounds are stored at -80°C or in liquid nitrogen. Once again, this is not critical, because companies that are able to handle products that need cold temperature storage have the means to do so.

QUESTION N°18: DO YOU HAVE ANY PARTICULAR STORAGE CONSTRAINTS?

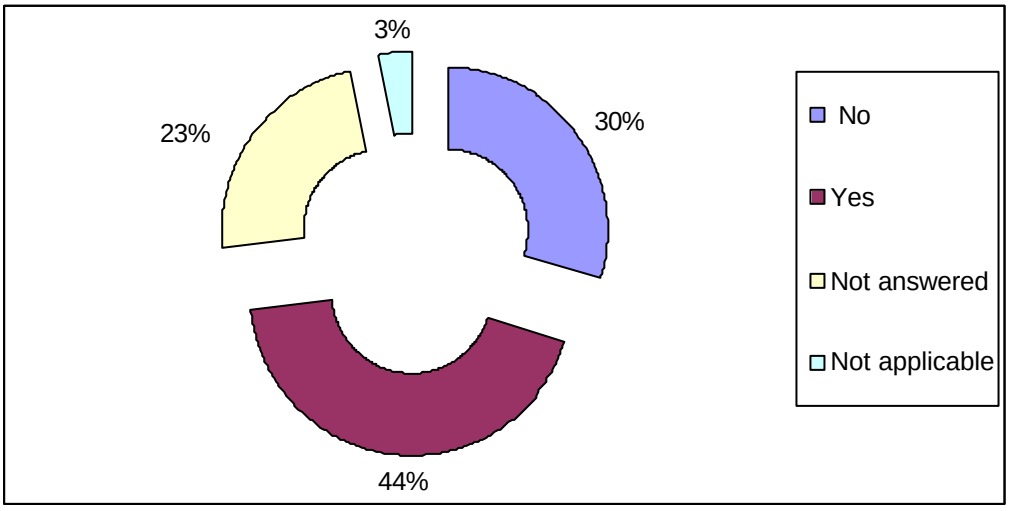
Storage constraints	Number of answers
No	11
Yes	8
Not answered	10
Not applicable	1



As for the previous question, storage constraints have to be appreciated with the type of manipulations related to the product. A company that is able to handle certain types of products is indisputably able to store them.

QUESTION N°19: DO YOU HAVE ANY CONSTRAINTS REGARDING THE TRANSPORTATION OF YOUR PRODUCTS?

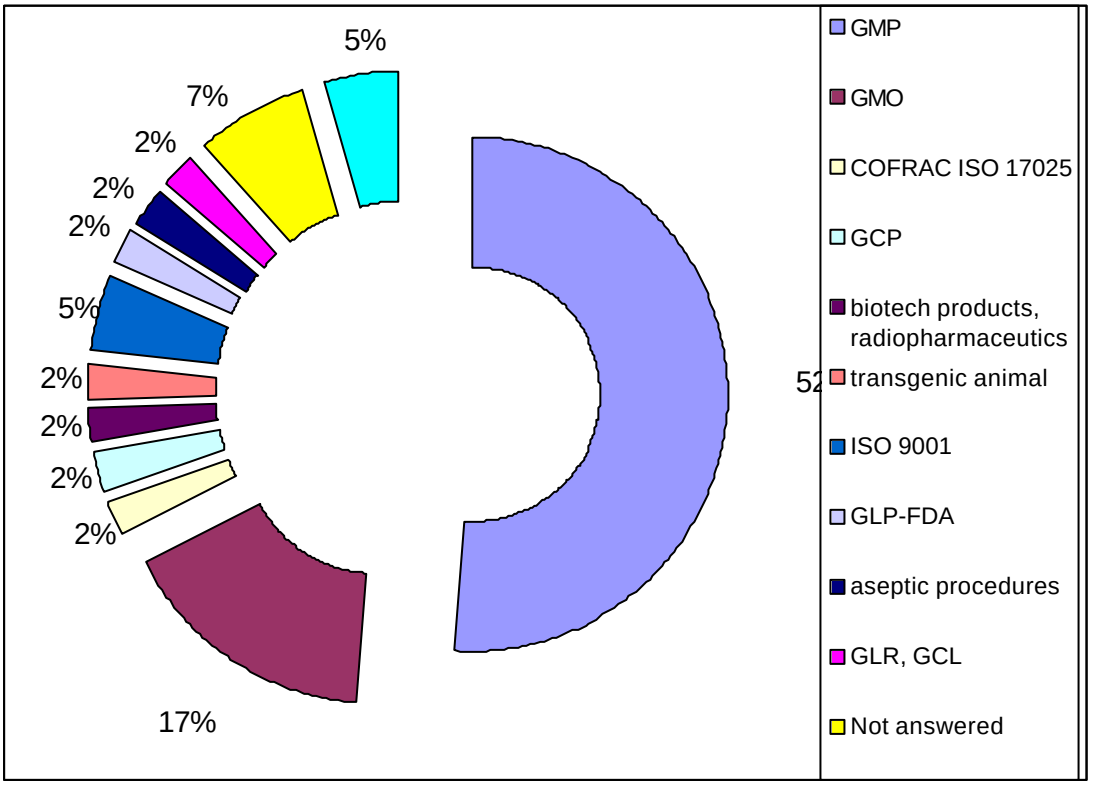
Transportation constraints	Number of answers
No	9
Yes	13
Not answered	7
Not applicable	1



The majority (44%) of expressed answers claim a need for transportation restriction regarding their products. However in a bio-manufacturing perspective, products transportation is usually not under a subcontractor's responsibility. So, this point just need to be clarified in the contract, but should not have any implication in terms of subcontractor's liability.

QUESTION N°20: ARE YOU SUBJECT TO ANY SPECIFIC REGULATION AND/OR LEGISLATION?

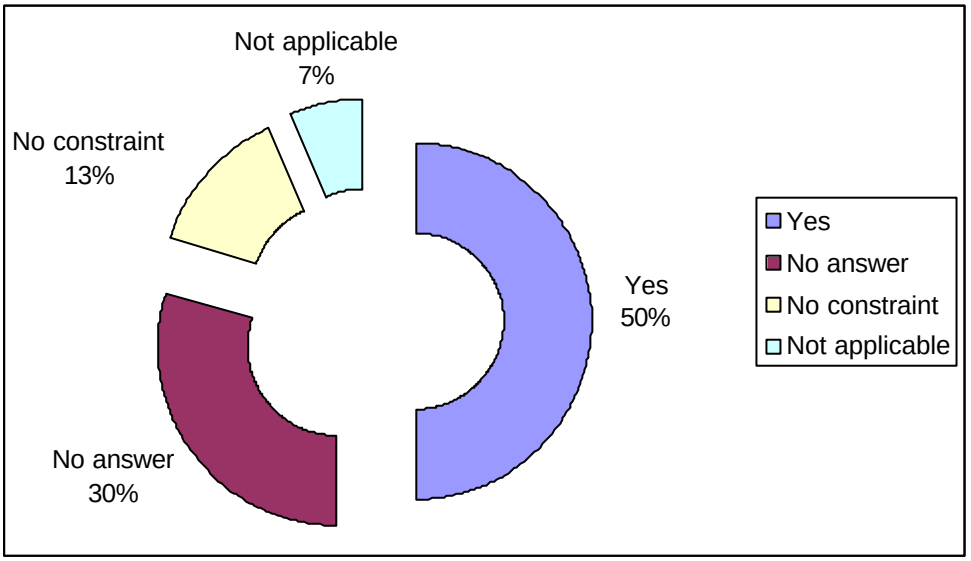
Specific regulation and/or legislation	Number of answers
Good manufacturing practice - GMP	22
Genetically modified organisms - GMO	7
COFRAC ISO 17025	1
Good clinical practice - GCP	1
Biotech products, radiopharmaceutics	1
Transgenic animal	1
ISO 9001	2
GLP-FDA	1
Aseptic procedures	1
GLR, GCL	1
Not answered	3
No constaints	2



69% of the biotech managers have quoted the two same regulations (GMP and GMO). Other regulations are very specific of particular domains. Apart from classical GMP/GMO regulations, the manufacturing of products for another biotech company supposes that the manufacturer is certified for handling the products. This can turn into a constraint and add to the segmentation of the biomanufacturing market, whereby not only subcontractors need to possess the techniques and the know-how, but also need to be in-line with all specific regulations required for each production.

QUESTION N°21: IS YOUR PRODUCTION PROCESS DIVISIBLE (BULK PROCESS, FINAL FILLING…)?

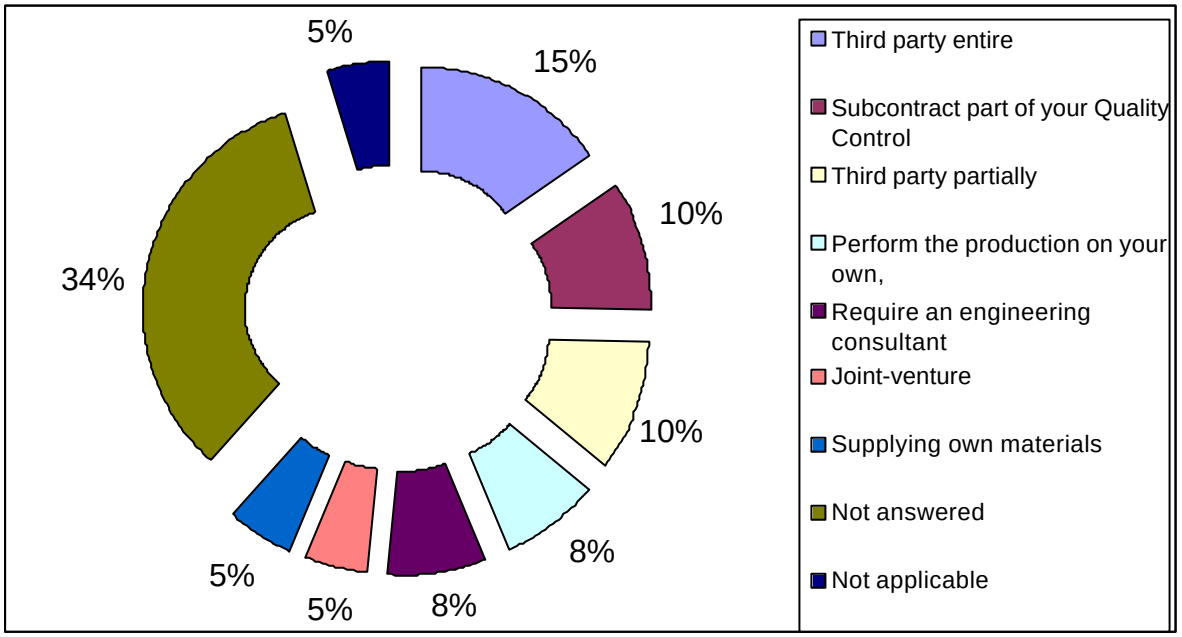
Process divisibility	Number of answers
No constraint (ask RB)	4
Yes	15
Not answered	8
Not applicable	2



Half of the biotech managers believe that their manufacturing process is divisible. This means that only some parts of the process can be subcontracted, thus implying flexibility. In this context, subcontracting a portion of the production can be easy-to-conceive and economically interesting, once there are companies specialized in specific products processing.

QUESTION N°22: IF YOU NEED TO SUBCONTRACT PORTIONS OF THE PRODUCTION PROCESS, WHAT WOULD THE INDUSTRIAL CHAIN LOOK LIKE?

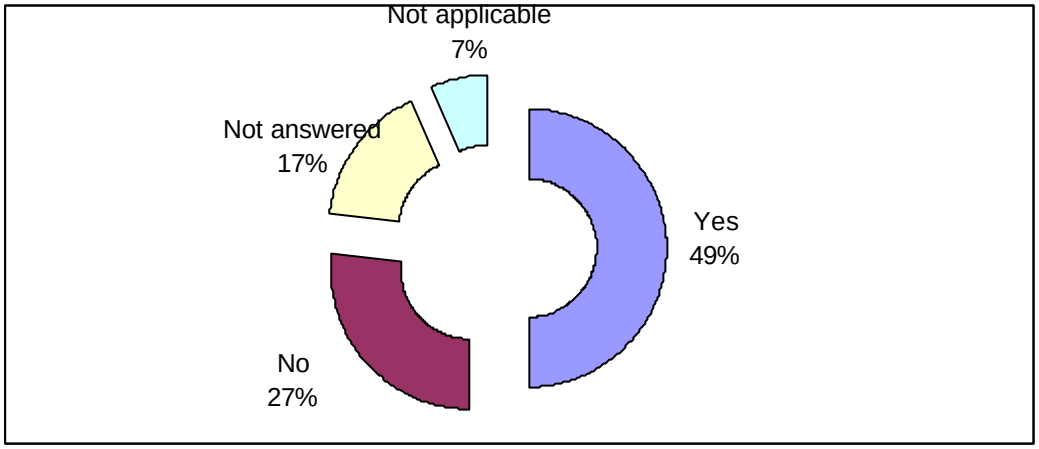
Industrial chain	Number of answers
Third party entire	6
Subcontract part of your Quality Control	4
Third party partially	4
Perform the production on your own,	3
Require an engineering consultant	3
Joint-venture	2
Supplying own materials	2
Not answered	13
Not applicable	2



The answers to this question also lead to ready interpretation. Many kinds of contractual schemes are imaginable and amenable to biotech managers. This can be understood as a need for high flexibility. Relationships between customers and suppliers can not be preset in a systematic framework. It can also be interpreted as a sign of immaturity. The lack of common usage shows that externalizing manufacturing is still not frequent in the biotech industry. However, the two last diagrams suggest the emergence of a highly-specialized but very flexible bio-manufacturing offer.

QUESTION N°23: DO YOU ANTICIPATE A NEED TO INCREASE YOUR PRODUCTION CAPACITY (IN-HOUSE OR SUBCONTRACTED PRODUCTION CAPACITY) IN THE NEAR FUTURE?

Production capacity increase	Number of answers
Yes	15
No	8
Not answered	5
Not applicable	2



Half of the biotech managers think that they will need an increase of their production capacities. This shows undoubtedly that there is room for the emergence of a biomanufacturing industry in France.

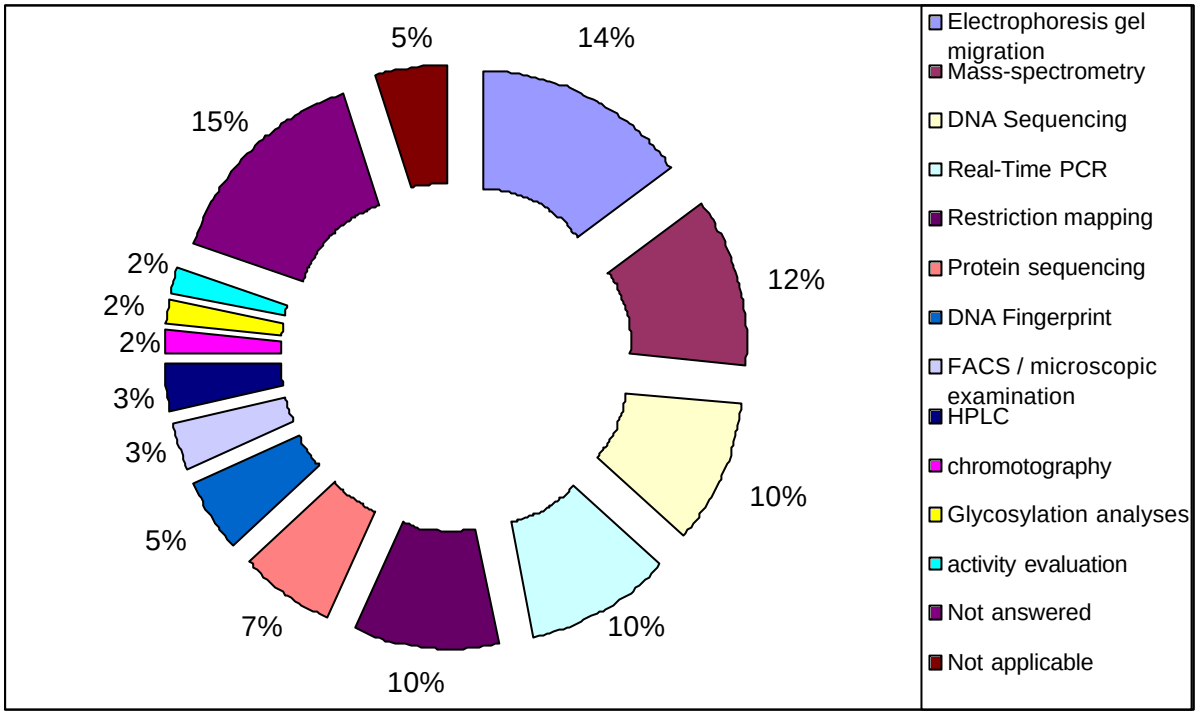
QUESTION N°24: WHAT IS YOUR ANNUAL PRODUCTION CAPACITY?

Extreme diversity or absence of answers to this question makes analysis worthless.

B. III Quality Control

QUESTION N°25: REGARDING QUALITY CONTROL OF YOUR PRODUCT, WHICH SPECIFIC METHOD(S) WILL YOU EMPLOY TO GUARANTEE IDENTITY?

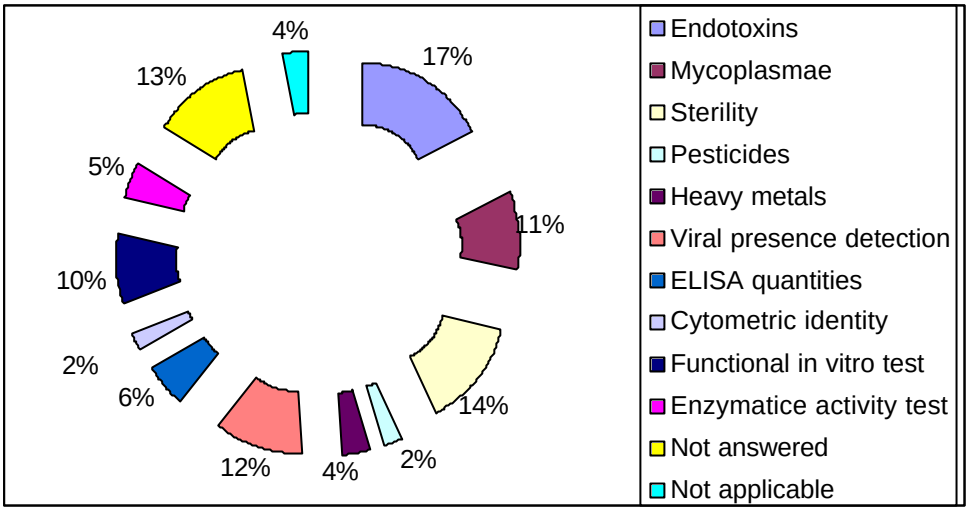
QC identity methods	Number of answers
Electrophoresis gel migration	9
Mass-spectrometry	7
DNA Sequencing	6
Real-Time PCR	6
Restriction mapping	6
Protein sequencing	4
DNA Fingerprint	3
FACS / microscopic examination	2
HPLC	2
Chromatography	1
Glycosylation analyses	1
Activity evaluation	1
Not answered	9
Not applicable	3



This diagram recapitulates the methods used to control identity. We get a fairly equivalent percentage (between 5 and 15%) for most techniques. This shows how connected to the nature of the product, the QC is. Subcontracting the identity control supposes to have a partner able to handle all kinds of tests, or most likely (if it will turn into a biotech-to-biotech business) to find a partner biotech handling the same controls for itself.

QUESTION N°26: REGARDING QUALITY CONTROL OF YOUR PRODUCT, WHICH SPECIFIC METHOD(S) WILL YOU EMPLOY TO GUARANTEE PURITY?

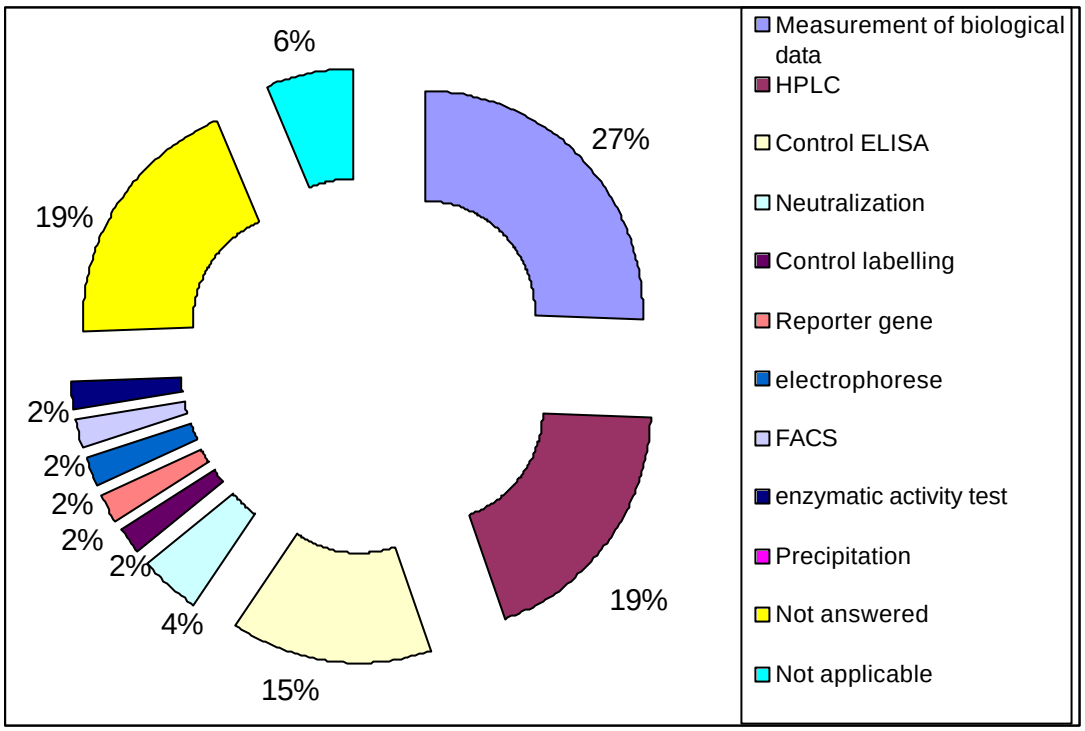
QC purity methods	Number of answers
Endotoxins	15
Mycoplasmae	9
Sterility	12
Pesticides	2
Heavy metals	3
Viral presence detection	10
ELISA quantities	5
Cytometric identity	2
Functional in vitro test	8
Enzymatic activity test	4
Not answered	11
Not applicable	3



Similarly to the previous diagram, purity can be controlled by using a large series of techniques. We can notice sterility and endotoxins (representing respectively, 14 and 17%) that are a bit more widely-spread than other tests.

QUESTION N°27: REGARDING QUALITY CONTROL OF YOUR PRODUCT, WHICH SPECIFIC METHOD(S) WILL YOU EMPLOY TO GUARANTEE POTENCY?

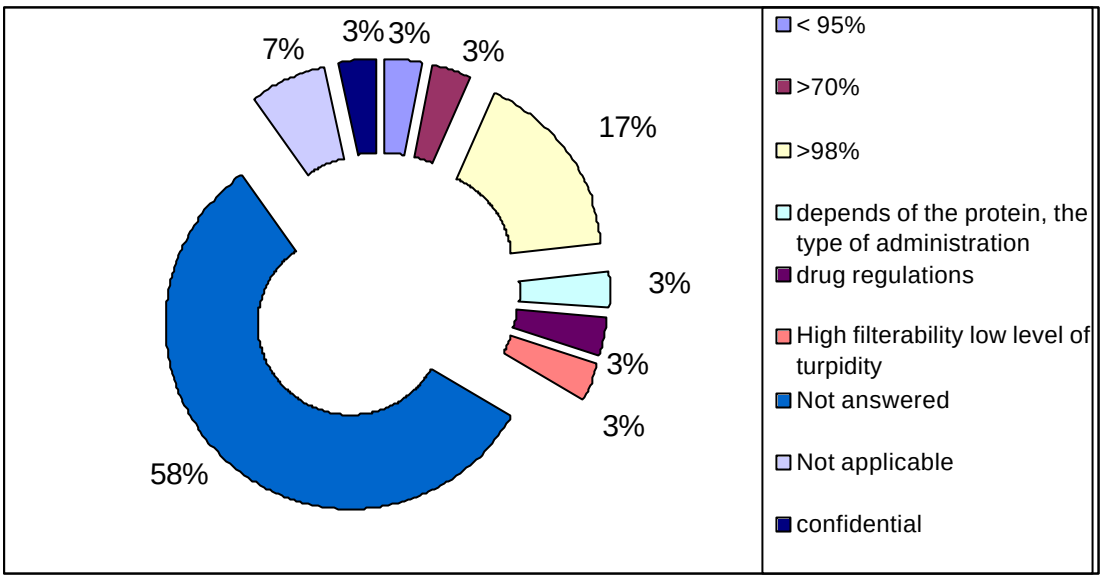
QC potency methods	Number of answers
Measurement of biological data	12
HPLC	9
Control ELISA	7
Neutralization	2
Control labelling	1
Reporter gene	1
Electrophoresis	1
FACS	1
Enzymatic activity test	1
Precipitation	0
Not answered	9
Not applicable	3



Potency testing differs slightly from identity and purity control. Three techniques (measurement of biological data, HPLC and control Elisa) among ten represent more than 60% of the techniques used. So, apparently potency is less specific than other QC testing, and therefore more easily subcontracted. This statement should be nuanced in that the most common technique (measurement of biological data) requires a know-how that is not easily transferable.

QUESTION N°28: WHAT WILL BE THE LEVEL OF PURITY REQUIRED?

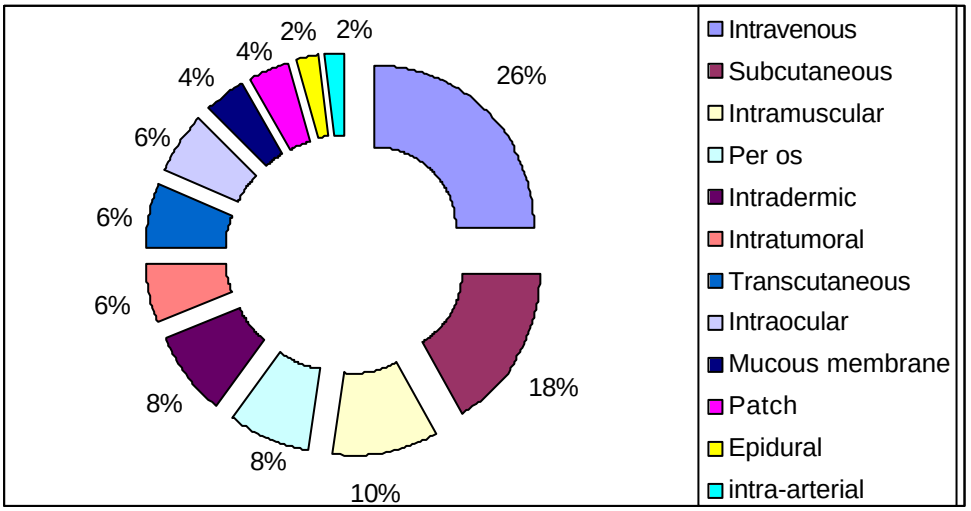
Purity level	Number of answers
< 95%	1
>70%	1
>98%	5
Depends of the protein, the type of administration	1
Drug regulations	1
High filterability low level of turbidity	1
Not answered	17
Not applicable	2
Confidential	1



According to the type of product and its applications, the level of purity required is very different thus necessitating specification in a contractual agreement.

QUESTION N°29: WHAT MODE OF ADMINISTRATION IS REQUIRED FOR YOUR PRODUCTS?

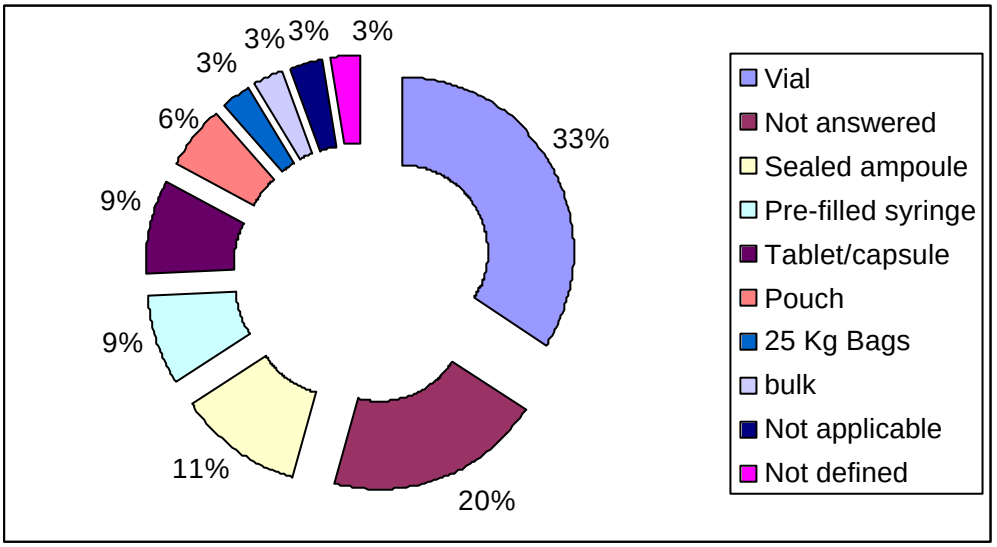
Administration mode	Number of answers
Epidural	1
Intratumoral	3
Intramuscular	5
Intravenous	12
Transcutaneous	3
Intraocular	3
Mucous membrane	2
Patch	2
Per os	4
Intradermic	4
Subcutaneous	8
Intra-arterial	1



If aggregated, all injected modes of administration represent more than 80%, compared to the other modes (*per os*, patch and mucous membrane) which reckon for less than 20%. Thus, injection dominates the market and therefore the administration mode is not as critical as a bio-manufacturing criterion.

QUESTION N°30: HOW WILL YOUR FINAL PRODUCT BE PACKAGED?

Type of package	Number of answers
Pouch	2
Pre-filled syringe	3
Sealed ampoule	4
Vial	12
Tablet/capsule	3
25 Kg Bags	1
Bulk	1
Not answered	7
Not applicable	1
Not defined	1



Although products are in most cases in liquid form (68%), packaging is very variable. This has numerous implications in terms of filling equipment, and can turn into an obstacle in identifying a manufacturing partner, able to handle a particular filling format. This adds to the tightness of specific partnerships that one encounters in the biotech industry.

C. Key-trends and recommendations

Interests and limitations of the study

The questionnaire was sent to the sixty members of France Biotech. Of those sixty members, thirty fully answered questionnaires have been received and analyzed. Refusals of biotech managers to respond to the questionnaire have been primarily for confidentiality reasons. Nonetheless, having a sample that represents 50% of the biotech sector is enough to extract the key-trends of the biotechnology manufacturing market in France.

The analyzable data mainly concern technical aspects (either scientifically or legally) of biotechnology manufacturing. Financial questions have often remained unanswered, thus restricting the scope of the study. Moreover, it would have been interesting to broaden the survey to the other actors of the biotech industry (venture-capitalists, state, regulatory authorities, industrial property agents, certain big pharmaceutical laboratories, etc.) This would have given a more accurate depiction of this market and its environment.

However, discussions that have occurred during the administration of the questionnaire and the analysis of data with both the biotech managers and the steering committee have complemented the study. Trends and recommendations that are listed below reflect not only the objective questionnaire-based data but also those informal discussions.

Biotechnology manufacturing in France: still immature?

The first lesson of this study is the relative inexistence of biotechnology manufacturing in France. There is no CMO remaining in France, and few biotech companies having filed the questionnaire, has claimed any incidental bio-manufacturing activity for the moment. In that sense, the market is still much undeveloped, even if a large percentage of companies already (Question 5 : 52%) know that they will need to subcontract their manufacturing in the future.

In comparison with traditional biotech activities dedicated to the discovery and the setting-up of new therapeutics, biotechnology manufacturing does not interest either venture-capitalist or the French government, according to many biotech managers. For the venture capitalist, biotech manufacturing suffers from a poor image in terms of return on investment. Although it is much less risky than the discovery of a new therapeutic agent, the French state, as for it, has not yet encouraged the development of this activity; perhaps because it is considered too remote from traditional academic research.

Elsewhere in Europe and North America, however, biological manufacturing is developing quickly. The two primary CMO's in the biotech industry are Boehringer Ingelheim (BI - Germany) and Lonza (Switzerland) but an increasing number of CMO's are emerging to take advantage and profit from the demand for high-volume therapeutic protein production. CMO's attending BioPharMOS 2003 in Monte Carlo, such as Dionsynth Biotechnology (UK), BioReliance (US), Q-One Biotechnologies (UK), Novozymes BioPharma (Sweden), and Strathmann Biotech (Germany) have either been recently created or have recently expanded their production capacity to meet the demands for biomanufacturing. Althea Technologies (US) has also followed suit in expansion.

French structural insufficiencies

As seen in the previous paragraph, the gap between France and other countries (even European countries) regarding biotechnology manufacturing is acute. Sorebio was the only recent biologics manufacturer existing in the French territory. It has now been purchased by Ares-Serono, and has since stopped its subcontracting activities. However, the inquiry clearly showed that several companies would have bio-manufacturing needs in the near future and will not have any other option but finding CMOs outside of France.

According to the inquiry, needs will concern mostly the purification of products, for which sophisticated techniques and specific know-how is requested. Simultaneously, the application in 2005 of the new European regulation about clinical trials, that requires the production of all clinical lots in GMP conditions, will make French biotech companies more and more dependent upon biotechnology manufacturers in other countries.

A necessary evolution

When asking Biotech managers, the manufacturing of products does not appear as a priority. Industrials are still focusing on R&D and clinical trials, in order to validate their leads. For biological products though, manufacturing questions are not easy to address and require early planning. This however is not today's preoccupation in most biotech manager's agenda. This lack of attention to future development issues should well merit special training of biotech managers on those matters. Because manufacturing of biotech products is clearly a strategic issue, a serious effort should be made to render biotech managers conscious of its importance.

The lack of answers on financial questions shows either a certain unawareness concerning the cost of manufacturing of bio-products. The classical comparison is to take the production costs of small molecules as the reference for bio-therapeutics. In fact, bio-products are from their very nature quite expensive to mass-produce, and require much more collateral investments (regulation conformity, safety and handling, quality control…) than simple chemical products. These costs should be taken into account sufficiently early when designing the product.

Similar to this poor awareness of manufacturing costs, the inquiry reveals much about how biotech managers imagine the type of relationships they will have with their biomanufacturers. In 85% of the cases **(table 6),** they imagine an outsourcing relationship, whereby the subcontractor will be a pure service provider. Biomanufacturing is crucial enough for allowing the subcontractor to ask royalties on the product, that he is manufacturing. In the US and in several European countries, sharing royalties with subcontractor is the common rule. Definitely, French biotechs are still very far from this conception of outsourcing business.

Organization of the market: future trends

Throughout the questionnaire, several elements indicate what could be tomorrow's biomanufacturing market. Logically, time-to-market of scientific innovation is extremely long (see table1). New therapeutic methods need 15 years or more to bring a product to the production lines which is nearly twice that for classical small molecules drugs organic synthesis.

Specific matching seems to be the key-feature of this emerging market. As a matter of fact, the inquiry has highlighted:
- The extreme diversity of technologies (see table1),
- The variety of therapeutics domain (see table 2),
- The number and multiplicity of technical steps,
- The constraints in terms of regulation (see table), storage or transportation,
- The accuracy of quality control methods of the biomanufacturing business.

In view of the breadth of such diversity, it is thus difficult to imagine that a single CMO would be able to handle all manufacturing techniques, fulfill all the requirements and manage all the

quality control tests. On the other hand, each company entering the biomanufacturing market would be obliged to focus on a certain type of technique, developing a specific know-how and investing in equipment strictly dedicated to a certain type of application. Biomanufacturing will likely be an extremely segmented market, where each player would set-up its own niche.

The relationship between the biomanufacturer and its client will then necessarily be very tight and critical. One could foresee the emergence of several small structures highly specialized in certain bio-industrial processes, corresponding to a certain type of demand. However, because techniques and needs evolve very quickly, those structures would need to be very reactive and be financially capable of the corresponding capital investments in order to follow the market trends.

The situation would be a bit different for companies, which would use their manufacturing capabilities mainly for themselves, but could think to act punctually as a subcontractor. In that kind of scheme, flexibility in terms of quality and quantity would be critical. The punctual subcontractor should be able to integrate rapidly small productions within its own manufacturing schedule, and operate a general process that could be easily adapted to its client-specific project.

This need for flexibility is reinforced by other replies to the questionnaire. In 50% of the cases (**see table),** the production process is divisible. This allows the outsourcing of specific segments of the production. This confirms the idea that there is room for several subcontractors highly specialized on certain process types. The second element, which goes in the same direction regards the legal framework of the potential collaboration **(see table).** The diversity of answers shows that there is no pre-defined contractual scheme. According to the type of production and its associated constraints, any type of collaboration is conceivable.

Proposals to meet identified needs

Subcontracting biomanufacturing is still at an embryonic stage in France. Nonetheless, the collected answers already give an insight of what could be this business tomorrow. They also suggest several measures to promote biomanufacturing in France:

-1- Biomanufacturing opportunities

According to the JP Morgan study, experts acknowledge serious concerns regarding the ability of biotechnology's current manufacturing capacity to meet current and future demand. Indeed, an increased concern is observed for biotechnology manufacturing capacity to meet demand now and in the near future. The following observation describes the apparent shortage in biotechnology manufacturing:

Most likely, companies which produce their own biologics and have unused manufacturing capacity will be well positioned to select and make lucrative in-licensing deals with smaller biotech companies that have inadequate or no manufacturing capabilities. Companies such as Biovitrum (Sweden) that traditionally produced their own clinical and commercial biologics have expanded their business activities to contract manufacturing. Biovitrum sells its unused manufacturing capacity to biotech companies who do not possess manufacturing capabilities or adequate manufacturing capacity to support their own clinical trials or commercial scales. Selling unused manufacturing capacity increases a biotechnology organization's operational effectiveness and profitability.

As a result, entering this market does not require to set-up a fully dedicated entity. Biotechs having products on their own can also diversify their activities by seizing biomanufacturing opportunities.

-2- State
To facilitate the emergence of this new industrial activity in France, the French government could play a key role. This has already happened in European regions such as Scotland or Bavaria, where an active supporting policy has been established to promote biomanufacturing activities.

Those regional initiatives have led to the creation of a viable industry that is not so dependent of research uncertainties. From the state point of view, promoting this industry means catching up and moving forward in a high-tech domain, encouraging the creation of a high value-added activity and developing highly qualified jobs.

Furthermore, since September 11th, 2001, this industry has turned strategic, in the sense that being able to mass-produce vaccines and antidotes against bio-terrorist agents is becoming a national security matter. For these reasons, it could be in the French state's interest to support bio-manufacturing, either through regional or national interventions.

-3- Financial markets
Now that we know that there will be an increasing demand in terms of biomanufacturing, we should see a shift in the financial markets' attitude towards biomanufacturing. Theoretically, less promising in terms of potential revenues than the traditional biotech industry, Bio-manufacturing investments appear more reliable and less adventurous. That is why they should trigger venture-capitalists interests in the near future.

-4- Matching organization
Because the market is very specialized, sudden, unstructured, it is comparable to a "spot market". Nonetheless, biomanufacturing seems to have a certain assurance for the coming decade or two, at least. If biomanufacturing needs are going to increase in Europe like the JP Morgan study suggests, there would be a need for an organizational structure that allows the matching of the demand and the offer. Opportunity could be accessible on the Internet as is already the case for most individual companies. There however appears to be still a need for an organizational structure to maintain and guarantee this effectiveness of exchange perhaps via a common internet site. This implies rapidly assuring the awareness broadly across the industry followed by the necessary conscious acts of training. This structure could be advantageously handled either by an inter-professional organization or a private structure.

-5- Cultural evolution
Key actions to be undertaken are providing training and information to all the actors of the French biotech industry. This implies rapidly assuring the awareness broadly across the industry followed by the necessary conscious acts of training of young technicians and managers able to work in this highly-technological sector.

Conclusion

This inquiry has given us a snapshot of today's biomanufacturing situation in France, a first and fundamental baseline from which to construct the future. Regrettably France clearly suffers a lack of interest of all actors of the field. It is unacceptable in a growing market, where France has not yet been able to position itself. In the near future, without concerted actions taken, not only France will have missed an interesting business opportunity, but also French biotechs might be confronted with the obligation to have their own products manufactured road. Today, the growth of the biomanufacturing market can and should be considered as an opportunity that should be seized by established biotechs as well as newcomers.

It would be useful to renew this kind of study on a yearly-basis or 2-yearly basis to disclose and evaluate those opportunities and their evolution. Setting-up a routine study of defined period would allow the follow-up of the French biomanufacturing market trends. The study would be then updated and would include chapters that are more specialized on certain techniques. This could become a helpful tool for Biotech managers to foresee their manufacturing needs in relation with the market production capabilities.

The other principle development axis would be to generalize the study to all Western Europe. From one country to the other, the situation is quite contrasted in terms of biomanufacturing --and thus the inquiry would maybe need to adapt to different situations. However, getting a picture of the European biomanufacturing market would enrich our vision of this economic activity and help all biotechs of the continent to find their partners and to target their market. Angelita de Francisco, who is in charge of France Biotech, has already been in contact with other partner organizations and will present this work at a future EuropaBio meeting to trigger a European collaboration on this issue.